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THE ANCIENT FACTORS IN THE RELATIONS BETWEEN THE BLOOD PLASMA AND THE KIDNEYS.[1]

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The animal organism, except that of the unicellular type, is a congerie of organs whose history, individually considered, as it is thus far revealed, constitutes the sciences we call comparative embryology and comparative physiology and which we must know, not only to comprehend the full significance of the work they now perform, but also to recognize and interpret the possible variants from the normal in function and structure which they may manifest. This history, in invertebrates as in vertebrates, is one of change either in structure or in function, or, often, in both structure and function, and, accordingly, frequently confusing and difficult to follow in any attempt to gain a full comprehension of the conditions and forces that determined the character of each organ.

One needs but to scan the list of the organs of the vertebrate body to illustrate how true this is. The nervous system with its protean manifestations in the line of evolution, the thyroid, the thymus, the suprarenals, the pituitary body, the pineal gland, the gills, the lungs, the alimentary canal with its accessory structures and even the liver, all have a past in which the dominant feature has been changed in structure and function with the result that the final stage in each transcends the earlier ones and so obscures their

[1] The Hatfield Lecture delivered before the College of Physicians, Philadelphia, April 10, 1917.

characters that it is now difficult to determine the earlier history except in some cases from the structural side.

One thing is indeed certain. The change has never been of the *per saltum* type. But it has been unceasing, without pause, and it is progressing today as it has been in the long past. The Heracleitan flux therefore plays its part in organogenic evolution as distinctly as it does in the physical world.

Among all the organs with their varied history as to structure and their variations in function, there is, however, one whose function in one particular respect has not changed from the time when it first began to evolve in the very far past. This organ is the kidney and the function which it performs, as it has performed it far back in the very beginning of the history of vertebrate life, is the regulation of the inorganic composition of the internal medium of the body, which we know as the blood plasma.

This organ was among the very first to appear in the protovertebrate, or in the first invertebrate type which began to differentiate along the line of development which resulted in the appearance of the protovertebrate in the Cambrian, or it may be pre-Cambrian times. If we may rely on the order in which the organs appear in the embryological history of the vertebrate, the renal organ is as ancient as the neural canal, and its origin would appear to antedate by a long period the closure of this canal and the disappearance of the coelomic cavity into which the primitive nephric tubules opened. If the latter are, as has been claimed, derived by differentiation from the coxal glands of a crustacean-like form, they are of more ancient origin than the neural canal itself.

What the kidney of the protovertebrate was we may gather from the earliest form of the vertebrate kidney, which consisted of three divisions, arranged in order from before backward: the pronephros, the mesonephros and the metanephros. One of these, the mesonephros, becomes the adult kidney in fishes and amphibia; another, the metanephros, becomes the functional kidney in other vertebrate classes, reptiles, birds and mammals. This is of significance, as I shall show later, in indicating that the regulation of the inorganic composition of the blood plasma exercised by the adult kidney must have been exercised also by the kidney of the protovertebrate.

In order to understand what this regulation involves we must for a moment consider what the inorganic composition of the blood plasma is. The salts of the blood plasma in amount range between 0.78 and 0.88 per cent. of the weight of the plasma, and they consist of the chlorides, phosphates, carbonates and sulphates of sodium, potassium, calcium and magnesium. The salts of sodium are by far the most abundant, after which come those of potassium, calcium and magnesium in the order mentioned. The salts of sodium, chiefly the chloride, amount to more than 90 per cent. of the total inorganic solids of the plasma.

The composition in detail has been determined by Bunge for the horse, ox and pig, and by Abderhalden for the ox, horse, pig, sheep, dog, cat.

The composition of human plasma has not been redetermined since 1850 when Carl Schmidt published the results of a number of analyses which are quoted now in all the text-books. They were obtained by the methods in use seventy to eighty years ago, which gave less exact determinations than those now followed in making such analyses, and, consequently, the percentages, notably those of potassium, calcium, magnesium and chlorine, which Schmidt's determinations yield, are open to question.

The inorganic composition of the plasma in birds, reptiles and amphibia has not been ascertained, but the total percentage of the ash has been ascertained to range between 0.8 and 0.9 in birds and reptiles, while in the frog it has been estimated to be as low as 0.46, but this may possibly be due to the difficulty of getting enough of the plasma of the frog free from admixture with water or lymph. The fact that in birds and reptiles the percentage of the salts is as high as in mammals is an indication that the details of the composition are not widely different from those of the plasma of the mammals above mentioned.

The analyses of the blood plasma in fishes which we have today are only those of the cod, pollock and dogfish, which I made eight years ago, and they are of special interest in connection with the analyses of the blood plasma of mammals.

If one examines Bunge's and Abderhalden's tables, giving the results of their analyses, one is impressed only with the fact that the details obtrude themselves to the exclusion of all else, that in fact one does not see the woods for the trees, and, in consequence, the significance of the results are obscured.

If, however, one selects the cationic elements and arranges them in values proportional to the most abundant one, sodium, which may be made equal to 100, order is obtained from the maze of details in these analyses, and one finds surprising resemblances in the values obtained from plasmas of all the mammals. Further, the proportions obtained from the analyses of the plasma of the fishes referred to fall into line with those from mammals in such a way as to suggest that we have thus revealed a cardinal feature in the inorganic composition of the blood plasma of vertebrates.

This feature is indicated in the following table of ratios in which Na = 100.

	Na.	K.	Ca.	Mg.
Dogfish (*Acanthias vulgaris*)	100	4.61	2.71	2.46
Cod (*Gadus callarias*) . .	100	9.506	3.93	1.41
Pollock (*Pollachius virens*) .	100	4.33	3.10	1.46
Dog	100	6.86	2.52	0.81
Mammal (average) . . .	100	6.69	2.58	0.80
Man (C. Schmidt) . . .	100	9.22	3.37	1.76
Man (A. B. M.)	100	6.11	2.71	0.85

The ratios for man are derived from Schmidt's analyses carried out, as already stated, with methods which were less exact than those which are employed today, and, in consequence, they are accepted with reserve, more especially as in my own determinations on the blood plasma of man the values for potassium, calcium and magnesium are much lower than those given by Schmidt and in general accord with those of Abderhalden and Bunge for mammals.

The ratio of potassium in the blood plasma of the cod, as determined in my own analyses, is high, but this may possibly be due to hemolysis, the preparation of serum which I used having a reddish tinge and therefore probably contained the potassium of the hemolyzed corpuscles, which thus would give a higher ratio for this element than would be given by pure plasma or serum. The fact that so near a relative of the cod, as is the pollock, gives less than half the ratio of the cod and approaches very closely that of the dogfish supports the view that the ratio in the cod is less than that given above.

Apart from these exceptions, if they are to be ranked as such and not due to errors in analysis or to abnormal composition, the striking feature is the very extraordinary parallelism between the ratios in mammals and those in fishes. This parallelism appears enhanced when one considers that the concentrations of inorganic salts in both classes of vertebrates differ. The concentration in the serum of the mammal, as already stated, ranges from 0.78 to 0.88 per cent. in the sera of the cod and pollock, from 1.282 to 1.293, respectively, while in the dogfish it is 1.774, or practically, double what it is in the serum of a mammal.

The parallelism in the ratios of the individual elements in the highest as well as in the lowest vertebrates is a cardinal fact, something more fundamental than the total concentration of the salts in the plasma. Its occurrence in two such widely separated classes of vertebrates suggests that it is an endowment received from the common ancestor of both, the protovertebrate, which must have existed in the early Cambrian or pre-Cambrian times.

What is the explanation of these ratios between the sodium, potassium, calcium, and magnesium?

The answer to this question I obtained some fourteen years ago when determining the inorganic composition of certain medusæ and comparing it with the composition of the ocean water of their habitat. *Aurelia flavidula*, the common jelly fish of our coasts in July and August, when it is liquefied, which happens when it is allowed to stand in a dry dish, furnishes a liquid in which, besides organic constituents, is contained a concentration of inorganic salts like that of the ocean water from which the animal was taken. From the analyses of its salts, compared with those of ocean water, ratios between the sodium, potassium, calcium and magnesium (with Na = 100) were obtained which revealed a very striking parallel.

	Na.	K.	Ca.	Mg.
Ocean water (Dittmar) . .	100	3.63	3.91	12.10
Aurelia flavidula (Macallum)	100	5.18	4.13	11.43

The parallelism between the two series of ratios is very close and the conclusion follows that the fluid in the tissues of *Aurelia* is but very slightly modified ocean water and of the same concentration as the latter.

It was, however, when the ratios for sea water were compared with the ratios of the blood plasma of a mammal, for example, the dog, that one obtained a clue to the origin of the ratios in the blood plasma of vertebrates. We see in the latter:

	Na.	K.	Ca.	Mg.
Ocean water (Dittmar) . . .	100	3.61	3.91	12.10
Dog (Abderhalden)	100	6.86	2.52	0.81
Limulus polyphemus (Macallum) .	100	5.62	4.06	11.20
Homarus americanus (Macallum)	100	3.73	4.85	1.72

that the ratios are parallel to those of ocean water, except in regard to magnesium. Were the ratio of the latter reduced to 1, or thereabouts, the parallelism between the two series would be so striking as to render unnecessary further discussion of the question of the origin of the ratios in the blood plasma.

That these ratios are of oceanic origin can admit of no doubt when we compare them with those of the horseshoe crab and lobster.

The horseshoe crab, *Limulus polyphemus*, which has had its habitat in the ocean since its origin in the early portion of the Palæozoic age, has a plasma in which the parallelism between it and ocean water is uncontrovertible. This is no doubt due to the fact that the osmotic pressure of the ocean has been acting on its plasma through the many millions of years which have elapsed since the Cambrian age, and, though unquestionably the ocean has been undergoing, in all that time, changes, not only in concentration but also in the ratios of its salts, the blood plasma of the horseshoe crab has kept pace with it and today the concentration of its salts equals that of the ocean water in which it lives, and the ratios in its plasma are practically those of ocean water. We thus see that ocean water does in this one case determine the inorganic composition of the blood plasma.

In the plasma of the lobster, *Homarus americanus*, which has been associated with the ocean only since the Cretaceous period, though the concentration of the inorganic salts is as high as the ocean water of its habitat, the ratio of the magnesium only is different from that of the ocean.

In both the lobster and the horseshoe crab the concentration of the inorganic salts of the plasma appears to vary with the concentration of the ocean water of their habitat, and in brackish water it falls to that of the latter. The concentration of the salts of the

plasma in these forms follows the concentration of the medium, whereas in the Selachians, which include the sharks and the dogfish and which have had their habitat in the ocean ever since the early part of the Palæozoic age, the concentration of the plasma salts exceeds half that of ocean water to a slight extent, although the osmotic pressure of the ocean has been exerting its effect on the Selachian plasma for at least several scores of millions of years. In the marine Teleostean fishes, which, like the cod, have been denizens of the ocean for a time, perhaps, not half as long, the concentration in the plasma is but little more than a third of the concentration of the salts in the ocean.

In the marine invertebrates of today the circulatory fluid is but a more or less modified form of sea water. In some the circulatory channels freely communicate with the exterior with the result that the circulatory fluid is pure sea water, but, even when the circulation is closed as it is in the horseshoe crab, the blood plasma is sea water with proteins and other organic constituents.

There is then a profound difference between the blood plasma of vertebrates and that of invertebrates. That of the latter varies more or less readily with an immediate change in the medium of the habitat, while that of the former is affected, and then but appreciably, only after millions of years.

Are we then to conclude that the plasma of vertebrates was primarily of origin different from that of the plasma of invertebrates?

If we scan the tables of ratios for the sodium, potassium, calcium and magnesium in the plasmas of the different forms of vertebrates and invertebrates, we see in the parallelism already referred to an unmistakable indication that the blood plasma of vertebrates was also originally sea water, not indeed the sea water of the present age, but of a far past when the concentration of its salts was less than one-third of what it is now and when also the potassium was relatively more and the magnesium relatively less abundant than in the ocean of today.

The sea is the original home of all life on our globe, and it was in the sea that the differentiation between animal and vegetable life as well as the evolution of the great divisions of the animal kingdom were effected. Indeed, the great events in the evolution of animal forms have been rendered possible by changes which have taken place in the composition of the ocean. Among the fundamental results of these changes was the development of a closed circulatory system of vertebrates, the fluid contained in which became henceforth independent of the composition of the contemporary ocean, and, as we have seen, of the ocean of subsequent periods even after many millions of years, as in the case of the Selachians (sharks), marine Teleosts (cod, herring) and the Cetacea (whales).

The sea ever since the first condensation of water on the original

cooled rock crust of our globe has been changing in composition by the leaching out of its bed the salts it contained and by receiving salts in the river discharge, also leached from the land areas of the globe. The quantity of salts annually discharged from the land areas is enormous and it is estimated by Joly at about one hundred and fifty-seven millions of tons (157,270,000), which, if divided into the amount of salts which he calculates as contained in the ocean today, namely, 14,151,000,000,000,000 tons, would give the age of the ocean as approximately ninety million years. The concentration has therefore been slowly changing and it must have been in the far past much less than it is now.

The relative proportions of the various salts must have changed also. All the salts discharged in the ocean by the rivers have not been retained, for, were they retained, the potassium and the calcium salts would be very greatly more abundant than they are now. Indeed the calcium salts in the ocean would have long ago reached a degree of high supersaturation quite impossible to conceive of, since the lime salts in the calcareous rocks of the earth's crust, deposited from sea water in the past ages, would thus be in solution in the sea. The potassium was, once, relatively to the sodium, more abundant than the present ratio indicates, and it has been and is being constantly extracted from the ocean in the formation of such minerals as *glauconite* apparently at a rate which keeps its concentration over long ages fairly constant. The magnesium salts also have been concentrating slowly, for the elimination of magnesium as carbonate in the formation of dolomitic limestone has been proceeding at a rate less than that of the constant addition through the river water. This would postulate that magnesium is not only absolutely but also relatively more abundant in the ocean of today than it was in that of the far past.

The only constituents that are not extracted from the ocean are the sodium salts. These have always therefore been on the increase from a time in the early pre-Cambrian when they were perhaps but slightly in excess of those of potassium. Their increase will proceed in the ages to come and finally produce such a degree of concentration and, consequently such a specific density that will, as in the water of the Dead Sea, permit the human body to float because of its lower specific gravity.

The differences in the series of ratios exhibited by the sodium, potassium, calcium and magnesium in the blood plasma of vertebrates on the one hand and in the sea water of today, on the other, parallel as these two series so strikingly are, can be explained as due to the blood plasma reproducing, approximately, the ratios obtaining in the ocean of the time when the original ancestral form of vertebrates, the protovertebrates, or eovertebrates, arose. The total concentration of the salts in the blood plasma can also be explained as due to a reproduction of the concentration of the sea

water of the same age, that is, when it had less than 1 per cent. of salts.

How far back in geological time this period was it is difficult to determine exactly. It must have been earlier than the earliest or most ancient fossil remains of vertebrates indicate, that is, in the earlier Cambrian or even pre-Cambrian, for the protovertebrate must have long preceded the vertebrates to which, through evolution, it gave origin. How long the intervening period has been is also difficult of determination. Estimates made on various bases give different results and the only satisfaction that one obtains from them is the recognition of their extreme limits, the maximal and minimal. Prof. Strutt in determining the content in helium of a mineral derived from Cambrian rocks of Renfrew County, Ontario, Canada, calculates that it was over seven hundred million years old. If, on the other hand, one follows Joly's method, based on the amount of salts in annual river discharge into the ocean, and the amount now in the ocean, and also accepting as approximately correct the percentage of salts in the ocean when the protovertebrate arose as less than 1 per cent., and therefore less than one-third of the concentration in the ocean of today, it follows that more than sixty millions of years must have elapsed since the protovertebrate appeared and disappeared on the geological horizon.

Whether we accept the higher or the lower estimate, or even a lower one still, the enormously long period during which the blood plasma has been simulating Palæo-oceanic conditions in the concentration of its salts and in the ratios of the sodium, potassium, calcium and magnesium it contains, emphasizes the importance in one respect of the organ which has maintained through the long ages of vertebrate history this concentration and these ratios, practically unchanged.

This organ is the kidney. There is in invertebrates no structure with a similar function or with a function even distintly approaching that of the vertebrate kidney. It is this organ that has made a fundamental difference between the vertebrate and the invertebrate, not only in the struggle for existence but also in the capacity to evolve higher forms of animal life. The animal form that must accommodate its internal medium to that of its habitat has an enormous handicap when it changes its environment, from ocean to fresh water or to land, as compared with one whose internal medium, under all circumstances, is constant in composition. With such a handicap vertebrate life and all that it involves would have been impossible.

This function of the kidney is fundamental and is more ancient than that of excreting the waste products of the tissues of the body. In the dogfish, as in Salachians generally, whose history has been associated with the ocean since their origin in the Silurian period and in whose blood plasma the concentration of salts has in

consequence been increased to only about half that of the sea, the difference between the osmotic pressure of the ocean water and that given by the salts of the blood plasma is equalized by urea which amounts to more than 2 per cent., and by ammonium salts, which amounts to more than $\frac{N}{10}$ reckoned as NH_3. This retention of urea and ammonium salts undoubtedly developed as a result of the tendency of the blood to balance the slowly increasing osmotic pressure of the sea water. The very fact that the kidneys in these forms exhibit inertness in the elimination of urea while they are extremely active in the elimination of salts is extremely significant. What they do most rigorously is the regulation of the inorganic composition of the blood, therefore the more firmly fixed physiological habit must be the more ancient one and, consequently, their earliest function was not the elimination of waste metabolic products but the regulation of the inorganic composition of the blood plasma. The function of excreting waste products developed later and in Selachians never acquired the fixity that characterizes the other function.

In the long ages the kidney has thus performed a function which for constancy and unvarying regularity is unrivalled in the world of life. This constancy, this unvarying regularity contrasts strikingly with the variation in function which the other organs have undergone and indicates how basic the kidney is in the vertebrate system and why it takes precedence in the body as a vertebrate organ *par excellence*.

How it happened that the kidney in the protovertebrate acquired this fixity of function we do not know. Geologists concede a very long time to the pre-Cambrian, a duration which, according to different estimates, ranged from one-third to nine-tenths of the whole geological period. In this long cycle of time many things could have happened and conditions must have obtained which impressed on the primitive kidney of the protovertebrate an abiding character, not to disappear even though the original organ underwent a marked transformation in structure before it developed into the renal organ of the vertebrate of today.

The question now arises, whether this Palæo-oceanic character is ever disturbed in disease of the kidney and, if it is, what are the results.

To this question there is not much to offer in the form of an answer. There have been very few investigations of the inorganic composition of the blood plasma in disease, and these only of a very limited scope, bearing almost wholly on the chlorine content, the amount of which was supposed to give an indication of the total concentration and of the sodium present. The conclusions based on such analyses are, of course, accepted only with reserve simply because of the tenuity of the data on which they are based. Plasma that are accessible are those of Schmidt.

Believing that the subject had possibilities in a clinical line, I undertook during the last five years investigations on the inorganic composition of normal human plasma, with a view to comparison of the same with the blood plasma in cases of Bright's disease, and, more especially, in cases of puerperal eclampsia. These investigations are not yet completed, owing to the time-devouring character of the work involved, but some of the results so far obtained are definite and interesting and they may be mentioned here.

It is to be premised, first of all, that the determinations in Schmidt's analyses, so far as sodium, potassium, calcium and magnesium are concerned, give too high values. Those for sodium range from 0.3173 to 0.3438 per cent. and for potassium from 0.0314 to 0.0332, while in my analyses the range of sodium is from 0.29 to 0.316 and of potassium from 0.019 to 0.0212. It may thus be seen that Schmidt's values are quite too high, and especially in the case of potassium, his average for the latter being 60 per cent. in excess of mine. The results obtained for the plasma in Bright's disease are quite incomplete, but those for puerperal eclampsia are far enough advanced to enable me to give some points of interest.

In 4 cases the ratios on the bases of Na = 100 were:

Cases.	Na.	K.	Ca.	Mg.
1	100	17.66	4.02	3.42
2	100	26.70	3.27	2.37
3	100	10.60		
4	100	10.10	2.59	0.68
[5 (normal)	100	6.11	2.71	0.85]

The magnesium and calcium content is high in Cases 1 and 2 and normal in No. 4, but in all the potassium is in excess and in No. 2 extraordinarily so, as much as four times the normal, while in No. 1 it is nearly three times the normal.

There was a minute quantity of hemoglobin in the serum of all the four cases, as revealed by the spectroscope, and some of the potassium found in excess of the normal may have been derived from hemolyzed red corpuscles which are rich in potassium salts, but this would not explain the excess in No. 2, in which the amount of hemoglobin in the serum did not exceed that in Nos. 3 and 4. It is possible that hemolysis in the circulating blood may be responsible ultimately for this excess, but this does not explain the non-elimination of the potassium in excess above normal by the kidneys. Temporarily, at least, in eclampsia the cellular elements of the kidney concerned in maintaining the normal ratio of potassium in the blood plasma must suffer a partial or total eclipse of function.

I am inclined to infer from the results of my observations that the very first change from the normal to the definitely established primary condition in some of the forms of Bright's disease is a loss of the power to maintain the Palæo-oceanic ratios.

The structures in the kidney involved in maintaining these ratios

are the proximal convoluted tubules, which, with the glomeruli, are derived from and therefore represent the original parts of the kidney of the earliest vertebrates and of the protovertebrates. The proximal convoluted tubules are also concerned in reducing the H-ion concentration of the blood, for they secrete acid, not acid salts, into the urine, a function which is also very ancient, a function performed in invertebrates by all the cells of the body situated near the body surface, and still performed intermittently and with a high degree of specialization by the gastric glands of vertebrates. In some invertebrates other tissues have specialized in this matter also, as for example, in the salivary glands of the carnivorous mollusc *Dolium galea*, the concentration of the sulphuric acid of the "saliva" of which exceeds 4 per cent.

It may be that the function of preventing the ever-tending-to-increase of the H-ion concentration of the blood plasma is as ancient as the Palæo-oceanic function, a view which their common localization in the proximal tubules supports.

Enough has been said here to emphasize the view that behind the functions of the renal organ is a history which links up the human body with the far past with an age of the earth when its oceans contained only what would now be regarded as brackish water and the earliest type of vertebrate life was just beginning to appear as a marine form. From the facts advanced it will be gathered also that the blood plasma, so far as its inorganic salts are concerned, is but a reproduction of the remotely ancient ocean, and that it is an heirloom from the life in

"that immortal sea
Which brought us thither,"

not indeed in the Wordsworthian sense, but in the literal one, for the sea is the original home of all life on the globe and gave our blood, and, accordingly, the tissues of our bodies, a character that long ages have not effaced and will not efface.

TYPHOID VACCINE IN A CASE OF TYPHOID SPINE.

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As only 30 out of the 104 cases of typhoid spine reported up to this time have been accompanied by roentgenograms, we feel justified in reporting a case with positive roentgen findings, and so

far as we have been able to discover, typhoid vaccine has not been used before in the treatment of this condition.

Few medical subjects have been so constantly and so thoroughly reviewed as typhoid spine, so that in reporting this case only a very brief summary of the development of our present knowledge on this subject will be given. Gibney,[1] in 1889, first called attention to the stiff and painful back which occasionally follows typhoid fever. However, his "Austrian Tyrol" case, with symptoms lasting two years, followed by permanent wry-neck, rather confused typhoid spine, with other types of spondylitis. Gibney reported this case to support his view that typhoid spine is a definite, infectious (inflammatory) process; this case is condemned by Lord[2] but approved by Halpenny.[3]

A few years later the waters were muddied when Osler[4] reported 4 cases of typhoid spine as simple neuroses. Inasmuch as postmortem pathology was not available in this condition, this conclusion could not be eliminated until some years later, when the roentgen rays began to demonstrate bony changes that are apparently responsible for the pain and the nervous symptoms. Lord, in 1902, reviewed the 26 cases reported up to that time, and concluded that the "pathology seems to be a perispondylitis or spondylitis, or both," and that although a few cases might be simple neuroses, "the coexistence of a deformity and nervous symptoms in one-half of the neurotic cases suggests that all the neurotic cases may be organic as well." At that time only Cutler's[5] case had been radiographed and no bony changes were found.

In 1905 Fluss[6] reviewed the subject, finding 46 cases. The next year T. McCrae[7] reported 2 cases with roentgenograms and was the first to give roentgenographic proof of the new-bone formation which usually occurs. Halpenny reviewed the subject very thoroughly down to December, 1908, summarizing 73 cases, and Elkin and Halpenny[8] have reviewed an additional 22 cases occurring up to the end of 1913, making a total of 95 cases.

In 1914 Conklin[9] and Job[10] each reported 1 case; in 1915 Galli,[11] Wilcox,[12] and Rugh[13] reported single cases and Carnett[14] reported 4 cases; we have found no cases reported during 1916.

Typhoid spine comes on within three months after typhoid fever

[1] New York Med. Jour., 1889, i, 596–598; Tr. Am. Orthop. Surg., 1889, ii, 19.
[2] Boston Med. and Surg. Jour., 1902, cxlvi, 26, 689–691.
[3] Surg., Gynec. and Obst., 1909, viii, 649.
[4] John Hopkins Hospital Bull., xxv, 265; ibid., iv, 73 and v, 315.
[5] Boston Med. and Surg. Jour., 1902, cxlvi, 26, 687–689.
[6] Centralbl. f. Grenzgeb. der Med. u. Chir., 1905, viii, 645.
[7] Am. Jour. Med. Sc., 1906, cxxxii, 878–889.
[8] British Jour. Surg., 1914, i, 4, 602–609.
[9] Med. Record, 1914, lxxxv, 4.
[10] Bull. et mém. Soc. méd. de hôp. de Paris, 1914, xxx, 990.
[11] Münch. med. Wehnschr., April 13, 1915.
[12] Colorado Med., 1915, xii, 7.
[13] Am. Jour. Orthop. Surg., 1915, xii, 2.
[14] Ann. Surg., April, 1915.

either suddenly or gradually, with pain in the back, which is apt to be severe. The character of the preceding fever is without significance. Three-fourths of the sufferers are males, and a history of more or less trauma is usually to be obtained. The lumbar spine is the site of election and the pain may radiate to the front of the body and down the legs. Movement of the spine is exquisitely painful, so that the back is held rigid, and sleep is very much broken by relaxation at night. Spasm of the muscles is frequent and abdominal rigidity has been observed. Carnett reports rhythmic contraction of the abdominal muscles. Tenderness over the spine is common, with occasional hyperesthesia, ankle-clonus, increased knee-jerks and muscular atrophy. After much suffering the victims become very neurotic. Half the cases have fever of an irregular type and the leukocyte counts reported have varied from 6000 to 17,600. About half the cases develop deformity, varying from slight prominence of one or several vertebral spines to marked kyphosis or scoliosis, a small number of these deformities being permanent. The duration of symptoms ordinarily is from three to five months, and no recurrences have been reported. Under rest, either postural or mechanical, tonics and the cautery all patients have completely recovered, except that in a small number permanent deformity with some limitation of motion has persisted.

In 11 cases of typhoid spine examined roentgenographically, reviewed by Halpenny,[15] the findings have varied from gross bony changes to none at all. Connor, Lovett, McCrae, Silver and Weigel report a total of 8 cases, with distinct changes of either the vertebræ, intervertebral disks or vertebral ligaments. Cutler and Petteshon in their cases found nothing abnormal. In 2 cases McCrae found deposits of new bone. In the first it filled the intervertebral space between the second and third lumbar vertebræ, apparently being deposited in the lateral ligaments and forming bony union; in the second the process extended from the second to the fifth lumbar vertebræ and appeared to involve both the lateral ligaments and part of the intervertebral disks. In the first of Myer's cases a synostosis between the second and third lumbar vertebræ, with loss of height from disappearance of the intervertebral space, was observed. In his second case there was clearly a synostosis of the eleventh and twelfth dorsal vertebræ, with diminution of height, owing to disappearance of this intervertebral space. In Silver's case the vertebral bodies seemed to be of normal thickness, but the space between them, corresponding to the disks, was absent, and the shadow of the first lumbar vertebra passed directly into that of the second; over this area there was increased density. On the right the lateral borders of the vertebral bodies formed an unbroken curved line; on the left there

[15] Loc. cit.

was an irregular shadow projecting outward between the transverse processes.

Elkin and Halpenny[16] review an additional 14 cases examined roentgenographically by various investigators, in 2 of which nothing was found. Of this series they cite Sireday's case, in which there was found thickening of the left side of the vertebral column of the second, third, and fourth lumbar vertebræ. In the other cases there were changes in the disks. Goddu found changes in the last dorsal and first lumbar vertebræ. Sweet found the disks gone between the fourth and fifth lumbar vertebræ and new-bone formation. McIntyre found the disk thickened between the fourth and fifth lumbar vertebræ and a deposit of new bone from the spine to the crest of the ilium; in his second case the fourth disk was thickened. Corling and Cain found a dense shadow on the sides of the ninth, tenth and eleventh dorsal vertebræ; a later roentgenogram of this was interpreted as an effusion beneath the periosteum and ligaments.

The cases reported by Wilcox and by Rugh and 3 of Carnett's cases showed the usual bony changes, while one of Carnett's cases showed nothing as late as the eleventh week.

In the case we report the roentgenograms show on the sides of the bodies of the second and third lumbar vertebræ a distinct clasp-like formation of new bone, producing a firm union and also a partial destruction of the disk and slight roughening of the body of the third lumbar vertebræ at the point of origin of the new bone. There is no evidence of involvement of any other vertebræ, though all were taken.

As demonstrated by the roentgen rays the early pathological findings consist in destructive changes in the bodies of the vertebræ, with absorption of the intervertebral disk; later there is proliferation of bone from the periosteum, with bony metamorphosis of the lateral ligaments. As first pointed out by McCrae, some cases may not reach the stage of new-bone formation, and roentgenograms may be negative early in the condition and positive later, as shown by Carnett's third case.

Case Report. Mrs. W., white, aged twenty years, married; cotton-mill operative. She was admitted to the Presbyterian Hospital December 5, 1916, complaining of severe pain in the left flank and over the whole region of the left hip. Her family and past history were unimportant, except that she had had an attack of typhoid fever beginning in June, 1916, and lasting for nine weeks. She returned to work in the mill in September. About November 1 her present trouble started as a "catch" in her left hip on walking. This pain became rapidly worse, spreading to her back and hip and thigh, so that she has been confined to bed for the past month. The

[16] Loc. cit.

least movement, as turning in bed, brings on painful spasm of the back muscles. At present the back is better but the pain over the hip and crest of the ilium is worse. From pain and loss of

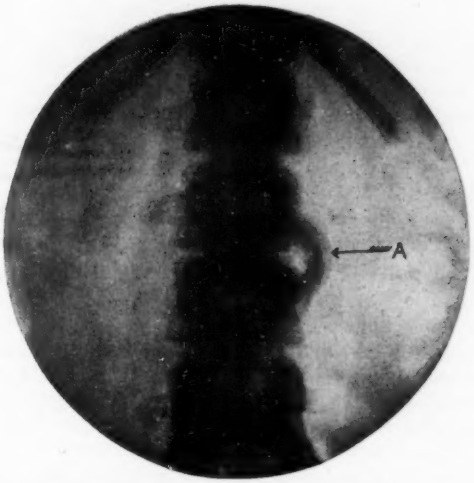

FIG. 1.—Clasp-like formation of new bone connecting second and third lumbar vertebræ.

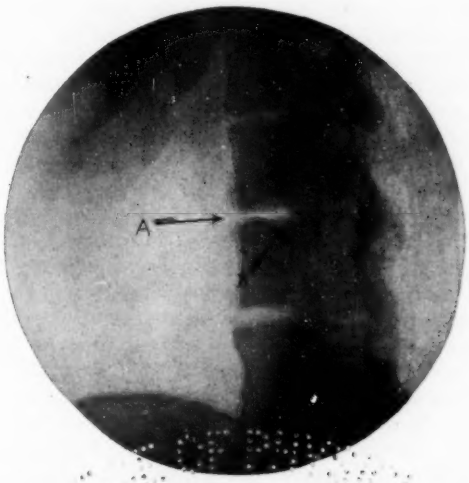

FIG. 2.—*A*, narrowing of vertebral slit from absorption of disk; *B*, area of erosion on body of third lumbar vertebra.

sleep she has lost appetite and flesh. Temperature from 99° to 100° on admission, with pulse 90 to 110. Her physician says that during the past month she has had high fever, reaching 103°, at times continuous, at other times intermittent.

Examination showed both upper and lower incisor teeth rotted off to the gums, with moderate inflammation of the gum margins. Eyes, throat, glands, heart, lungs, abdomen, skin and reflexes normal. No real or apparent shortening of the left leg. Trochanter below Nélaton's line. Motion of hip-joint normal. The motion of the lower half of the spinal column is very limited indeed. Moderate motion backward and to each side, all causing pain referred to left iliac crest. Cannot bend forward at all. Even when standing quietly the vertebral column is overextended and inclined to the left, with the left lumbar muscles spastic. Gait normal. Palpatation over left lumbar back and ilium painful. Sacro-iliac joint not sensitive.

Flexion of extended legs on body equally limited on both sides because of the pain this produced in the back. Jarring the soles of both feet caused pain in the left lumbar region. Roentgenograms of all the teeth and the pelvic bones were normal. The changes in the second and third lumbar vertebræ are shown in the accompanying roentgenograms.

The back was strapped with adhesive and the usual immunizing doses of a commercial mixed typhoid vaccine were given. After the first dose, December 10, the temperature, which had been running from 99° to 100°, remained normal. After the second dose, December 14, she was allowed to return home, and was able to sleep through the night without pain. The third infection was given December 19, at which time the improvement was marked. Reported December 27, showing the back much improved; anxious to go to work.

January 17 the back was no longer painful and motion not much limited. Allowed to return to work. Roentgenograms showed no increase in bone formation.

February 16, she has worked without difficulty, except that her back tires more easily than formerly. No pain and no deformity. Very slight limitation of motion, with about 5 per cent. decrease in efficiency of the back. Roentgenograms showed no further changes.

Conclusions. It is difficult to estimate the value of the typhoid vaccine in this case, as the process was subsiding spontaneously. However, the temperature remained normal after the first dose, and there was a marked decrease in the pain the day after the second dose. From the clinical history of typhoid spine it seems probable that typhoid vaccine given early, would stop the development of this local infectious spondylitis.

ELECTROCARDIOGRAPHIC EVIDENCE OF ABNORMAL VENTRICULAR PREPONDERANCE AND OF AURICULAR HYPERTROPHY.[1]

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and

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The present communication summarizes a clinical investigation undertaken to define the electrocardiographic limits beyond which one may conclude the presence of abnormal ventricular preponderance and of auricular hypertrophy.

It has first been necessary to establish an index for the calculations. The following satisfactory formula was finally employed: the measurements are of the amplitudes of the string excursions expressed in tenths of a millivolt (millimeters on the photographic records):

$$(U_1 + D_3) - (D_1 + U_3) = I,^2$$

where I signifies *index*, U_1 signifies the amplitude of the chief upward excursion of the QRS group in Lead I_3, and D_3 signifies the amplitude of the chief downward excursion of the QRS group in Lead III; D_1 and U_3 are interpreted correspondingly.[3] For example, if U_1 measures 16 millimeters, D_1 3 mm., U_3 5 mm., and D_3 22 mm., the index $= (16 + 22) - (3 + 5) = +30$; if U_1 equals 4 mm., D_1 18 mm., U_3 19 mm., and D_3 0 mm., the index equals $(4 + 0) - (18 + 19) = -33$.

An increase of the index in the positive direction indicates a swing of the electrical axis to the left either from actual change in cardiac position or from increase of left muscle mass in the heart itself; a change toward the negative values indicates a swing of the electrical axis to the right.

For controls we have examined 100 normal people: 60 young male adults, 20 young female adults, 20 children under nine years of age and 20 old people over sixty-five years of age. Dr. E. B. Krumbhaar has kindly sent us his table of measurements[4] of 41 children and we have also used the figures of Lewis and Gilder[5] in

[1] Read in part before the American Society for Clinical Investigation, Atlantic City, N. J., May 1, 1917. The call to active service abroad delays the publication of a detailed report of this investigation with complete tables.

[2] A similar formula was mentioned by Lewis, Heart, 1914, v, 398.

[3] The average of several successive beats should be taken to avoid respiratory variations in amplitude.

[4] This table has since been published in Heart, 1917, vi, 189.

[5] Philosophical Transactions of Royal Society, 1912, ccii, B. 351.

their study of 52 normal young male adults. Our high positive and negative indices have been found among 1100 cases electrocardiographed at the Massachusetts General Hospital.

It was of considerable interest to note in the case of the electrocardiogram of old age that not infrequently the index was nearer the average normal value than that of a number of the healthy children with relatively high positive values. When a decidedly high positive value was found in an old person, marked arteriosclerosis, hypertension or aortic regurgitation was also found. It would seem then that old age *per se* does not give a characteristic electrocardiogram.

The individual electrocardiogram is remarkably constant, as a rule, in the value of the index. In 12 cases the maximum individual variation over periods of three months to two years was found to be +4. In a few cases, more particularly those with aberrant ventricular complexes, as in bundle branch block with progressive heart disease, there may be considerable variation: 3 of our cases —all with aberrant ventricular complexes—showed variations of −25, −17 and −34 in the index over periods of five months to two years. Electrocardiograms of cases such as these cannot be used in the estimation of ventricular preponderance.

In the course of this investigation it was found by comparison of electrocardiograms with fluoroscopic tracings that cardiac position has an important bearing on the index, and a respiratory test has been used. The position of the heart as determined by the type of the individual being studied, for example, squat or lanky, very likely affords the explanation for the occasional discrepancies between ventricular weights and electrocardiograms. Incidentally it may be noted here that the position of the diaphragm has much more influence on the inclination of the actual cardiac axis, and therefore on the electrocardiographic index than have pneumothorax or pleural effusions. These, if large, generally push the heart *in toto* to one side or the other with little or no change in the inclination of the axis; if there is a change in the axis it may actually be due to a greater displacement of the base than of the apex.

By the use of the preponderance index described above in the electrocardiographic study of 1200 individuals, values of +20 and −15 have been found to be close to the border-line of normality (Tables I and II). Indices of +20 to +30 and of −15 to −18 have usually indicated left and right ventricular preponderance respectively and those beyond +30 and −18 have always indicated ventricular preponderance in our series. The highest values in normal people indicate, as a rule, unusual cardiac position; for instance, a fairly high positive value in a short, fat person really indicating a horizontal position rather than left preponderance and a fairly high negative value in a tall, long-chested individual indicating a

"vertical heart." The respiratory test which by inspiration lowers the diaphragm and straightens the heart and by expiration acts in the opposite way is useful in the analysis of doubtful cases. Left ventricular preponderance in a short-chested person would give rise to an electrocardiogram of exaggerated left ventricular preponderance.

P deflections over 3×10^{-4} millivolts in amplitude or over 0.1 second in duration almost always indicate the presence of auricular hypertrophy (Table III).

TABLE I.—TABLE OF LEFT VENTRICULAR PREPONDERANCE.

Index of preponderance.	Total number of cases.	Aortic regurgitation.	Blood-pressure of 180 mm. or more without aortic regurgitation.	Aorta dilated or roughened without aortic regurgitation or hypertension.	Miscellaneous.
Above +30 .	21	9	12	0	
+20 to +30 inclusive	61	22	18	11	10 (8 normal)
Total . . .	82	31	30	11	10

Respiratory test on 10 of first three groups; index of 8 stayed high. Index of 5 of last group became normal with respiratory test.

TABLE II.—TABLE OF RIGHT VENTRICULAR PREPONDERANCE.

Index of preponderance.	Total number of cases.	Mitral stenosis.	Rheumatic mitral disease without stenosis.	Pulmonary stenosis (congenital heart)	Chronic emphysema.	Normal.
Beyond −18 .	15	9	2	3	1	0
−15 to −18 inclusive	7	4	0	0	0	3
Total . . .	22	13	2	3	1	3

TABLE III.—ENLARGED P DEFLECTION.

Over 3×10^{-4} volts in amplitude, or over 0.1 sec. wide, or both.

Total number of cases.	Mitral stenosis.	Rheumatic mitral disease without stenosis.	Hyperthyroidism.	Miscellaneous.	Right ventricular preponderance index of −15 or beyond.	Preponderance index minus.
70	21	5	1	1 with paroxysmal tachycardia. 1 with paroxysmal auricular fibrillation. 1 with syphilis.	11	19

One case with +17 had aortic stenosis as well as mitral stenosis.

CHOLESTEROHYDROTHORAX, OBSERVATIONS UPON A CASE.

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(From the Department of Medicine, Cornell Medical College Dispensary, and the Department of Clinical Pathology.)

The problem of cholesterol metabolism commands a position of increasing interest to the medical profession today. Many striking facts about cholesterol have been collected through recent experimental studies, but a clear understanding of its role in human physiology has not yet been attained. For this reason it would seem important that all new or unusual data upon the subject be made matter of careful record.

The occurrence of a large quantity of cholesterol crystals in a pleural effusion is certainly a rare enough phenomenon to merit such attention. Since I observed this phenomenon several months ago I have been unable to discover a clinician or pathologist who remembers ever having seen or heard of such a case. This circumstance led me to a careful search of the medical literature, in which I have found astonishingly few observations of the kind recorded.

In 1908 Ruppert[1] reported a case of his own in which he had found cholesterol crystals in the pleural fluid. At that time he could find but two other similar cases in all the literature. After a thorough review of the medical literature since then I have been unable to add any other cases, although the subject of pleurisy, as well as that of cholesterol, has received particular attention.

In the various classifications of pleurisies made recently by French and German authors (Patein,[2] Chauffard,[3] Méhu,[4] Halipre,[5] Müller,[6] Schlesinger[7] and many others), based upon thousands of analyses, there is no mention of the occurrence of free cholesterol. Patein in describing a rather rare type of pleural effusion, which he terms chyliform, states that in some of these small quantities of cholesterol had been recognized by chemical analysis. Also in the cases of true chylothorax, recently reviewed by Lewin,[8] a small quantity of cholesterol was regularly encountered. But this alimentary cholesterol, coming directly from the lacteals of the mesentery, bears no relation to such deposits as the one here considered. Likewise in the analyses of over 300 pleural fluids, made in the Cornell labora-

[1] Münch. med. Wchnschr., 1908, lx, 510.
[2] Jour. de Pharm. et de Chem., 1915, (s. 7), xi, 265.
[3] Presse Méd. (Paris), 1915, xxiii, 341.
[4] Arch. Générale de Méd., September, 1881, ii, 257.
[5] Presse Méd., August 19, 1905, 523.
[6] Jour. de Méd. internat., 1906 (s. 221).
[7] Ztschr. f. klin. Med. u. Kinderheilkund., 1914, xiii, 138 (bibliography).
[8] Am. Jour. Med. Sc., 1916, cli, 71.

tory of clinical pathology, where one case of chylothorax is recorded, there is no mention of any case of cholesterohydrothorax.

The patient who furnished the data of this report appeared on February 17, 1916, in the Cornell medical dispensary.

CASE HISTORY.—*Family History.* William Delaney, aged fifty-one years, one of ten children, was born in Ireland of healthy parents. There is no record in his family of hereditary diseases nor of any metabolic disturbances, such as gout, diabetes, extreme obesity, nor of any other morbid peculiarities, such as prevalence of gall-stones, of early apoplexy, of goiter, gigantism or acromegaly.

Early History. He was "always healthy" throughout childhood, youth and early manhood, subject to no catarrhal diseases, and except for measles at the age of six or seven years was never sick in any way until thirteen years ago.

Marital. He is married, the father of five healthy children, one other having died in infancy, cause unknown.

Venereal. A questionable lesion on the penis twenty-three years ago; no subsequent luetic manifestations. Gonorrhea twenty years ago; no sequelæ.

Occupation. Has worked steadily as a carpenter since boyhood.

Previous Illness. Thirteen years ago, in 1903, while engaged at work in a dusty, poorly ventilated tobacco factory his health began to fail. He recalls few symptoms. "Just kept going down hill." Coughed very rarely as he remembers, and complained of no definite pain. He continued working for two or three months, and when he finally consulted a doctor he was immediately sent to Bellevue Hospital. Here his left chest was aspirated and 94 ounces of fluid removed. The character of this fluid could not be definitely ascertained, as the record of his admission could not be found, but the patient asserts that it was quite clear and of a slightly yellowish tinge. He was very weak after the aspiration, but insisted upon going home the next day. A few days afterward he returned to work and kept hard at it in spite of his feeble condition. He felt "rocky and all played out," as he puts it, for a long time, but was determined to work it off. Apparently his condition did improve somewhat, for he did not have to stop working again until four years later, in 1907. At this time he had an attack of what he called "dry pleurisy." He cannot remember a distinct chill, but the attack came on suddenly, with a cough and pain in the left side. He had a high fever, was in bed five weeks, delirious part of the time and was attended upon several occasions by a private doctor.

Again, he went back to work in the early period of convalescence and worked hard without cessation up to the present time. His strength was greatly reduced, and very little exertion would make him short of breath. Occasionally he suffered pain in the chest, and every winter was tormented by a persistent cough.

Dietary Considerations. During the last seven or eight years, practically ever since the last severe illness, the patient has noticed that pork does not agree with him. It destroys his appetite for a number of days every time he eats it. The fat of beef is well borne, he declares, in respect to its effect upon appetite and digestion, but it always acts upon him as a cathartic. Eggs have likewise disagreed with him, in every form except as a single one added raw to a glass of milk. He relishes kidney stew but seldom indulges in it, and he cares little for fresh vegetables. His favorite food, and, indeed almost constant diet for many years, has been beefsteak and potatoes.

Habits. He always drank beer and ale in generous quantities, but little whisky until five or six years ago, when he began to use it steadily, often to the exclusion of food, and in gradually increasing amount. For a long time he drank three or four glasses a day. He believed it strengthened him for his work, consequently as his health failed more and more he increased it to six or eight glasses. Thus his tolerance became high. He was never "drunk," but kept steadily at work all this time.

Tobacco. He was an excessive pipe-smoker for many years, but a moderate smoker now.

Present Illness. On February 2, 1916, patient was forced to quit work, and on the 17th he applied at the dispensary. His dyspnea had steadily increased and was aggravated by a chronic cough, worse at night, productive of a moderate amount of tenacious, whitish sputum. He had had no hemoptysis, no chills or fever; his appetite had been getting poorer each day. Bowels were regular.

Physical Examination. A tall, scrawny man, aged fifty-one years, appearing older, quite gray already, somewhat stooped and decidedly emaciated, with suggestion of alcoholism in the facies, heightened by a considerable degree of congestion and cyanosis of the nose and other extremities. Height, 6 feet 2 inches; weight, 132 pounds. Breathing rapid and shallow: rate, 32. Tempertaure, 98.7° F. The skin shows only early senile changes. *Head:* normal brachycephalic calvarium. *Eyes:* moderately advanced arcus senilis, pupils unequal in size and irregular in outline, but react well to light and accommodation. *Teeth:* poorly preserved; gingivitis present. *Tongue:* slightly coated and tremulous. *Neck:* negative. *Thorax:* long and narrow, with limited expansion, more marked on left side. *Lungs:* the characteristic signs of left-sided pleural effusion. Behind the dulness extends to the midscapular region and to the side it coalesces with the left cardiac dulness. There is some harshness of breath sounds over the right upper lobe and scattered subcrepitant rales over both lungs. There is hyperresonance over the right lower lobe, the base of which extends to the level of the twelfth spine. *Heart:* area of cardiac dulness cannot be determined on the left; to the right it extends 3 cm. beyond the external margin

of the sternum. There is a soft systolic murmur at apex and base, not transmitted, and the first sound at the apex is short and relatively weak. *Pulse:* regular in rate and rhythm, of fair size, rather poorly sustained, no increased tension. *Blood-pressure:* systolic, 150; diastolic, 100. *Arteries:* thickened and extremely tortuous, the pulsations in brachials plainly visible. *Abdomen:* slightly convex, musculature, in good tone, no resistance about gall-bladder or elsewhere; no masses felt. The liver edge can neither be felt nor percussed beneath the costal margin. The first evidence of deep hepatic dulness, in sitting and reclining posture, is reached at the level of the sixth rib, in the right midclavicular line, actual flatness first at the seventh rib, one inch below the level of the tip of the xiphoid. The flatness can be traced downward a very short distance, a little over an inch. In the anterior axillary line the liver flatness begins at the ninth rib; in posterior axillary, at the tenth; behind, at the level of the twelfth spine. The first change of deep percussion is approximately one inch above this plane. The vertical extent of hepatic dulness, in the midaxillary line, is about two inches. *Spleen and kidneys:* not palpable. *Extremities and deep reflexes:* normal.

Radiograph of chest confirms the diagnosis of left-sided hydrothorax, and reveals, besides, a number of moderately dense, rather diffuse shadows in the upper right lobe, interpreted as tubercular in character, also a sharply defined, dense shadow, about the size of a hazel nut, in the left chest, on the level of the ninth rib, apparently a calcified node.

Sputum: negative for tuberculosis. *Urine:* normal amber color; specific gravity, 1020; faintest trace of albumin and very rare hyaline casts; no sugar. *Blood Wassermann*, negative.

On April 5, 1916, the left chest was aspirated. In the midst of the operation, certainly before more than two-thirds of the fluid had been withdrawn, dragging pain in the left chest became so severe and the pulse so weak that an abrupt termination was necessary. After aspiration the dulness was considerably diminished but still quite distinct as high up as the angle of the scapular behind and to the cardiac apex in front.

The singular appearance of this fluid excited immediate curiosity. It was yellowish gray in color, quite turbid, and peculiarly glistening in reflected light, filled with tiny, scale-like particles, which, upon the least agitation, circulated about, imparting a beautiful satin-like sheen to the surface of the fluid. The fluid was quite odorless, with a faintly salty taste. Upon standing the suspended particles sank promptly to the bottom and the volume of this gray sediment was almost as great as that of the now translucent supernatant fluid.

Microscopic examination, confirmed by the sulphuric acid color test and the qualitative reaction of Salkowski, identified the glittering scales as cholesterol crystals.

There were very few other formed elements present, a few large

cells, evidently of endothelial origin, and an occasional smaller cell, probably leukocytic. All of these cells showed abundant fatty granules, and there were many other such granules floating free in the fluid. No cells were encountered that did not show degenerative changes. No red corpuscles, nor shadows of such, could be found. No bacteria could be discovered by the usual staining methods, and aërobic cultures on broth and agar were negative.

The volume of the fluid was 1200 c.c.; specific gravity, 1023; albumin (Kjeldahl), 6.69 per cent. Total cholesterol (after saponification of esters), 1.39 per cent.[9] Fatty acids, 33 per cent.[10] Lecithin was present in very small amount, but not estimated.

The cholesterol of the blood was determined by Csonka's[11] modification, of the Autenrieth-Funk[12] colorimetric method. This was done on May 6. One cubic centimeter of the whole blood contained 2.5 mg. of cholesterol. Two days later blood was drawn, allowed to clot and the fresh serum pipetted off. This was found to contain 3 mg. per cubic centimeter. A serum of a normal individual, done at the same time as a control, contained but 0.7 mg.

A large quantity of urine was extracted with ether and tested by the same delicate method, but showed no trace of cholesterol.

Since the first paracentesis on April 5, 1916, two other aspirations have been performed. In the first of these, on April 18, the same severe pain and shock interrupted the operation very early in its course; but in the last, May 6, it was possible to withdraw all the fluid that would flow.

The second pleural fluid was not analyzed. The cholesterol crystals, still abundant, were not nearly in such proportion as at first.

The third fluid was still poorer in cholesterol. The crystals were smaller and many of them had lost their characteristic form and sharpness of outline. The relative proportion of fatty granules and fatty degenerated cells seemed to have increased. The fluid was less turbid but of a darker amber hue. Specific gravity, 1020; albumin (Kjeldahl), 3.85 per cent. Cultures of this fluid, on several media, by anaërobic as well as aërobic methods, were negative.

A considerable amount of pain about the heart and left pleura followed the aspirations, but at the same time there was a gratifying improvement in the patient's general condition, with abatement of cough, easier breathing, better appetite and increased strength.

Definite dulness and impairment of breath sounds at the base of the left lung persisted after the last aspiration, and was attributed

[9] Measured quantity of material, saponified under reflux, with alcoholic KOH, neutralized, extracted with ether, dried residue extracted with petroleum ether, vacuum dried and weighed.

[10] Method of Gephart and Csonka, Jour. Biol. Chem., 1914, xix, 521.

[11] Jour. Biol. Chem., 1916, xxiv, 431.

[12] Münch. med. Wchnschr., 1913, No. 23, lx, 1, 1243.

to probable thickening of the pleura. These signs had not changed noticeably when the patient was seen a month later.

Two years ago Schlesinger made a very thorough study of the pleurisies of old age, and in his exhaustive article he emphasized the frequency with which advanced sclerotic changes are found in the pleural membranes of the arteriosclerotic and senile. Pic-Bonnamour[13] emphasized the same point. A general thickening of the membranes, with spots and streaks which often attain cartilaginous consistency (*the plaques du frottement*, overlying the ribs), atrophy and obstruction of the blood and lymph vessels, as well as degeneration of the lymph glands at the hilum, are the significant changes noted. That these regressive changes are in large measure responsible for the diminished resorptive power of the membranes, and therefore for the frequent occurrence of long persistent effusions in the aged, is hardly to be questioned. Furthermore, it has been discovered that in the exudative pleurisies of old age hemorrhagic effusions are relatively frequent (Crepin), while, according to Schlesinger, seropurulent effusions are found in about 33 per cent. of all cases. This means that the disintegration of cellular exudates within sclerotic, pleural cavities is in nowise an uncommon process. But such disintegration necessarily results in the release of the cholesterol constituent of the cells. In fact, this cellular disintegration is the commonly accepted explanation of the cholesterol deposits found in old pus cavities, in tubercular masses and in old cysts. Yet common as is this process of chronic pleural effusion with cellular disintegration, deposits of cholesterol crystals are not often found. Evidently some other factor, which has not yet been recognized, is concerned in the production of this phenomenon. A brief consideration of the data of the other recorded cases might furnish some important suggestion upon this point.

The earliest case, reported by Churton[14] in 1882, was that of an English laborer, aged thirty-eight years, who had suffered for several years with serous pleurisy and who died in the hospital, after numerous aspirations, with empyema. The pleural exudate, rich in cholesterol crystals (percentage not determined), contained also an abundance of red and white cells. There were no other significant facts recorded.

The second case was briefly mentioned in Rosenbach's treatise upon the diseases of the pleura in Nothnagel's *Handbuch*. In an autopsy upon a non-tuberculous woman he found a mass of cell detritus, blood pigment and cholesterol crystals in a ten-year-old encapsulated, pleural effusion. Neither age nor history of the patient was given.

The third case, reported by Ruppert in 1908, was that of a much depleted, alcoholic vagabond, who had had a pleural effusion twelve

[13] Paris, 1912, O. Doin et fils, 904, p. 8°.
[14] Tr. Clin. Soc. (London), 1882, xv, 19.

years previously, and upon date of examination was suffering with dyspnea on exertion and pain in the chest. This case was reported in much greater detail than the other two. Both the clinical and pathological findings, so far as they were noted, conformed closely with those of my case. The accompanying table will show the similarity of the exudates:

Case.	Amount, c.c.	Specific gravity.	Albumin (Kjeldahl), per cent.	Total cholesterin, per cent.	Fatty acids, per cent.	Cultures.
Ruppert	1750	1025	6.60	1.29	0.36	Sterile.
Weems	1200	1023	6.69	1.39	0.33	Sterile.

Such close conformity as these two cases display would strongly bespeak an identical underlying condition, but examination of the data does not reveal what this condition is.

The histories of these 3 cases are so incomplete and the clinical observations so meager that no common factors can be discovered upon which a satisfactory explanatory hypothesis might rest. There certainly appears to be small likelihood of a purely anatomical pathological basis for the condition of cholesterohydrothorax. A much more likely basis would seem to be a peculiar disturbance of cholesterol metabolism. Although we may not discover the exact nature of this disturbance a review of the subject of cholesterol metabolism, with this purpose in mind, should be of decided interest and profit.

Almost without exception, in those conditions in which abnormal infiltrations or deposits of cholesterol occur, *e. g.*, pregnancy,[15] diabetes,[16] obesity,[17] chronic nephritis, arteriosclerosis, eclampsia, jaundice and xanthelasma, a hypercholesterolemia has been found.[18 19 20 21 22] Such habitual coincidence of two factors cannot but suggest a direct relationship between them. Other evidence in support of this suggestion is not far to seek. The figures of blood cholesterol determinations, made under a great variety of conditions, reveal the fact that the fluctuation of this substance in the blood is confined within comparatively narrow limits. The normal figure set down by Klinkert,[18] later confirmed by Bacmeister and Henes,[17] and now practically established, is 1.5 to 1.8 gm. per 1000. Figures under 1 and over 2 are considered abnormal. The highest figures reported by Klinkert are for chronic parenchymatous nephritis, 4.26; for

[15] Hermann and Neumann: Wiener klin. Wchnschr., 1912, xxv, 1557.
[16] Klemper and Umber: Ztschr. f. klin. Med., Berlin, 1907, lxi, 145; 1908, lxv, 340.
[17] Bacmeister and Henes: Deutsch. med. Wchnschr., 1913, xxix, 1, 544.
[18] Berl. klin. Wchnschr., 1913, l, 1, 820.
[19] Fischer: Virchows Arch., 1903, clxxii, 20 and 218.
[20] Weston and Kent: Jour. Med. Research, Boston, 1912, xxvi, 47 and 531.
[21] Grigaut: Various arts. in Compt. rend. and Semaine Médical.
[22] Iscovesco: Compt. rend. Soc. biol., Paris, 1912, lxxii, 225.

diabetes with marked acidosis, 4.965; for pregnancy, 4.25. In spite of conditions most favorable to the accumulation of large quantities of blood cholesterol, such, for example, as complete biliary obstruction, the high-level mark of 5 gm. per liter of serum is very rarely attained; while it is very commonly observed long before this unusual concentration is reached, that abnormal infiltrations of cholesterol have already appeared in various tissues of the body. Thus, xanthelasma, a cholesterol-ester infiltration of certain cells in the skin, frequently appears during the hypercholesterolemia of pregnancy, to disappear gradually as the blood cholesterol sinks to the normal. The same holds true for the retinal white spots[23] (cholesterol-ester) in eclampsia, in chronic nephritis and in diabetes mellitus. Moreover, Windhaus[24] has shown us to what an enormous extent cholesterol deposition takes place in the walls of the arteries during the progress of atherosclerosis, with which a hypercholesterolemia is always associated.

Experimental evidence of this nature was first adduced by the Russian investigators. Anitschow[25] showed that rabbits fed upon a cholesterol-rich diet develop a condition of the arteries quite analogous to human arteriosclerosis, with similar deposition of cholesterol in the vessel walls. Dogs who normally possess a greater power of metabolizing and eliminating cholesterol could not be so affected. By feeding rabbits pure cholesterol, Anitschow and Chalatow[26] rapidly raised the cholesterol level of their bloods and produced a cholesterol infiltration of nearly all the organs of their bodies.

The increase of cholesterol-ester in the adrenals, when the blood cholesterol is increased, a fact carefully studied and demonstrated experimentally by a great number of observers (Hueck,[27] Knack,[28] Wacker and Hueck,[29] Sternberg,[30] Borberg,[31] and others), has never been satisfactorily explained, but seems to stand largely upon the same basis as the phenomena produced by Anitschow.

Hoesli[32] produced in rabbits with hypercholesterolemia a skin lesion closely related to xanthelasma, in which the young fibroblasts became laden with cholesterol and cholesterol-ester. But nothing of the nature of xanthomatuberosum could be produced. Weil,[33] in a study of the significance of giant-cell tumors of the tendons and joints, found the uniform presence of hypercholesterolemia. He concluded that there is no essential difference between xanthoma of the skin and the tumors in question. Both, he believes, represent

[23] Lauber and Adamuk: Arch. f. Ophth., Leipsig, 1909, lxxix, 429.
[24] Ztschr. f. physiol. Chem., Strassburg, 1910, lxvii, 174.
[25] Ziegler's Beitr., 1913, lvi, 379; Deutsch. med. Wchnschr., 1913, xxxix, 741.
[26] Centralbl. f. allg. Path. u. path. Anat., 1913, xxiv, 1.
[27] Verhandl. d. Deutsch. path. Gesellsch., Jena, 1914, xvii, 149–156.
[28] Virchows Arch., 1915, ccxx, 36 (bibliography).
[29] Arch. f. exp. Path. u. Pharm., 1914, lxxviii, 432.
[30] Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 91; ibid., 1914, lx, 114.
[31] Skandin. Arch. f. Physiol., Leipsig, 1914, xxxii, 15–287.
[32] Brun's Beitr., 1914, xcv, 198.
[33] Berl. klin. Wchnschr., 1915 (No. 6), 129.

infiltration processes on the basis of a general disturbance of cholesterol metabolism in which the one presents a mild tissue reaction and the other an energetic reaction.

The experimental facts strongly support the view that the various mentioned forms of tissue infiltration serve, to a large extent at least, as channels of vicarious elimination of cholesterol, when that substance reaches an intolerable concentration in the blood. The exact mechanism of this tissue infiltration, especially in the human cases, is a question of the greatest interest and importance, but one upon which, up to the present time, very little light has been thrown. The presumption is strong, however, that some other factor besides the high concentration of blood cholesterol is involved in the production of the phenomenon. The deposition of cholesterol-esters seems closely analogous to the production of gouty tophi. That the deposition is preceeded in both cases by a toxic injury to the cells is certainly a probable hypothesis. That such injury and deposition may occur without hypercholesterolemia is suggested by the report of Rosenbloom,[34] who was unable to find hypercholesterolemia in a pronounced case of xanthoma multiplex. By both the clinical and experimental facts, however, it seems firmly enough established that the blood cholesterol cannot be pushed beyond a certain level without provoking, somewhere in the body, a tissue deposition or infiltration.

The fact that with the dog, accustomed as this animal is to a cholesterol-rich diet, feeding experiments failed to produce cholesterol infiltration of the tissues or even to raise, to any appreciable extent, the level of the blood cholesterol, while both these phenomena could readily be achieved with rabbits, led to the tacit assumption that the difference was due to the greater deësterizing power in the liver of the dog. But this unwarranted assumption is contradicted by the only direct experimental testimony so far presented. D'Amato,[35] feeding large quantities of lipoids to dogs and measuring the cholesterol of the bile, found that only a small fraction of the excess was thus excreted. The rest, he was forced to conclude, was otherwise disposed of in the organism. Comparing D'Amato's discovery with the common clinical observation that in pregnancy, although the cholesterol content of the diet may be unchanged and basal metabolism lowered, there is, nevertheless, an increase in the cholesterol content of both the bile and the blood, we are led to conclude that the animal organism possesses the power of converting into some other form a greater or less quantity of cholesterol, and that this function is considerably less in the pregnant than in the non-pregnant state. It is interesting to note that up to the present time the most widely accepted theories of cholesterol metabolism have not accepted this conclusion.

[34] Arch. Int. Med., October, 1913, xii, 395.
[35] Biochem. Ztschr. (Berlin), 1915, lxix, 217.

In an extensive series of researches upon the chemistry and metabolism of cholesterol, Lifschütz[36] has disclosed some strongly presumptive evidence in support of the theory that the nitrogen and sulphur-free constituent of the bile acid salts is derived quantitatively from cholesterol. He presents good grounds, moreover, for the belief that the first step in the process consists in the conversion of cholesterol into oxycholesterol. This latter substance he has identified in most of the tissues of the body. He looks upon this preliminary oxidation of cholesterol as a purely chemical reaction, taking place for the most part in the blood stream. He has demonstrated the reaction in mixtures of oxyhemoglobin and cholesterol dissolved in acetic acid, and has further shown that the power of these hemoglobin solutions to oxidize cholesterol is greatly reduced, if not entirely inhibited, by the presence of more readily oxidizable substances such as the lower alcohols. In spite of the original and painstaking character of Lifschütz's work and the vital nature of its evidence it seems to have been largely ignored by the numerous other investigators of the physiological chemistry of cholesterol.

Just what becomes of a deposit of cholesterol in the tissues has been the subject of considerable curiosity. Basten[37] found that cholesterol injected under the skin of rabbits causes prompt necrosis, followed rapidly by granulation tissue and the appearance of large cells, which take up the crystals in the form of cholesterol-esters. Corpor[38] carried out the same experiment in guinea-pigs, finding that the deposit gradually disappears. Klotz and Bothwell[39] injected a mixture of cholesterol and oil into the veins of rabbits, producing obstructive lesions in the lungs, in which phagocytic cells eventually appeared ingesting the oil and cholesterol, in the form of tiny globules, of which some were anisotropic, *i. e.*, cholesterol-esters. That the initial step in the removal of cholesterol from the tissues is represented by its ingestion by giant cells in the changed form of cholesterol-esters has been repeatedly demonstrated. What next becomes of this cholesterol-ester, investigation has not positively determined. The assumption is well-nigh universal, however, that as ester or in uncombined form it finds its way eventually into the blood stream. But there is no convincing proof that chemical change does not occur within the cells. That such change might be controlled by intracellular oxidases is a speculation that cannot be lightly discarded. The demonstration of oxycholesterol in the various tissues by Lifschütz is to be considered in this relation.

Once incorporated in the blood stream all authorities agree that a part of the cholesterol is eliminated by the liver and excreted in the

[36] Frequent Articles from 1907 to 1914 in Ztschr. f. phys. Chem. and Biochem. Ztschr.
[37] Virchows Arch., 1915, ccxx, 126.
[38] Jour. Biol. Chem., 1912, xi, 37; Jour. Exp. Med., 1915, xxi, 179.
[39] Proc. Soc. Exp. Biol. and Med., 1915, xii, xciv, 159.

bile; another part, it is as generally agreed, is utilized as an indispensable constituent in the manufacture of new cells; but the theory that a third part, and quite a considerable proportion, is oxidized in the blood stream and converted (probably by the liver) into the N- and S-free constituent of the bile acids seems at present to enjoy the support of a single authority.

It is the writer's opinion that future investigation will establish the theory that the N- and S-free constituent of the bile acids is derived from the oxidation of cholesterol and that the oxidation takes place, not as a simple chemical reaction, as supposed by Lifschütz, but under the regulation of a ferment (perhaps a product of internal secretion) in the same way as the other special oxidative processes of the body, disturbances of which are exemplified in hypothyroidism and pregnancy. The case herein reported lends some support to this view. Its various features are not readily explicable upon the basis of any other theory yet advanced. The inability to digest any considerable quantity of fat, in association with an unusually small liver, naturally suggests a deficient liver function, specifically a deficient secretion of bile salts. It is quite conceivable that the long and excessive use of alcohol (alone or in connection with some other factor) might serve to impair the cholesterol-oxidizing-ferment or to divert it from its normal function, thus diminishing the production of the N- and S-free constituent of the bile acids. However effected, any reduction of cholesterol oxidation would presumably result in an increase of that substance in the blood, a result which could only be enhanced by the heavy intake of the meat-rich diet upon which my patient chiefly subsisted. With the constant cholesterol saturation of the blood thus produced it seems to some extent reasonable that the accumulation in the pleural exudate could not be absorbed.

This tentative explanation is presented for whatever suggestive value it may possess, with the hope that it may stimulate a keener interest in a subject which is rapidly acquiring greater clinical significance.

THE CHEMOTHERAPY OF LEPROSY AND TUBERCULOSIS.

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Introduction. Robert Koch, in 1890, stated that auricyanide is toxic for tubercle bacilli, although it has no effect on animals not infected with tubercle bacilli. Bruck and Gluck stated, in 1913, that potassium auricyanide is efficacious for lupus. Von Linden and Meissen employed the iodomethylene blue and copper lecithin compounds, both intramuscularly and cutaneously, in the treat-

ment of tuberculosis patients, and succeeded in establishing certain favorable results (1913). Strauss obtained good results with the use of iodomethylene blue and copper potassium tartrate injected intravenously and also applied cutaneously (1913). Bodmer recommended copper lecithin, especially in combination with tuberculin. Demark recognized the value of injections of electrocuprol. The effect of copper salvarsan on persons suffering from tuberculosis and leprosy was investigated by Shiga, in 1915, with certain good results. Favorable results were also obtained by Koga, in 1915, with potassium cuprocyanide, prepared by himself and tested on tuberculous men and animals.

The writer has undertaken an investigation of the chemotherapy of leprosy and tuberculosis, with the results here set forth.

Agent and Form of Application. The agent, which I have called potassium cuprocyanide, is a combination of 2 parts of potassium cyanide and 1 part of cuprous cyanide, and is in the form of small white, needle-shaped crystals, which are soluble in water and alcohol. Five mg. per kilogram of body weight is the lethal dose for the rabbit.

Dose. The patient received an injection of a 0.1 to 1 per cent. of the aqueous solution every ten days, the amount injected being equivalent to 0.25 to 0.3 mg. per kilogram of body weight.

Results of Treatment in Leprosy. One to three injections of the agent produce the following effects in leprous patients:

The nodes gradually become soft, or begin to bleed, after which they diminish in size or are resorbed, in time completely disappearing. The leprous ulcers heal and form scars only after two or three injections. They lose their characteristic color eventually. Sensory disturbances are also overcome when the swollen nerves have had time to shrink to their normal size. The treatment frequently has the effect of stimulating the growth of hair in areas where it has fallen out. A summary of the results of the use of the agent in leprosy is as follows:

AFTER 1 TO 3 INJECTIONS (TO JUNE 5, 1915).

	Cases.
Diminution or disappearance of nodes	17
Drying up, cicatrization or healing of ulcers	2
Improvement of vision	2
Temporary increase in size of nodes	4
No change in symptoms	11
Total	36

Continued injections often produced remarkable effects. Injections given in the case of other forms of leprosy were also productive of good results.

Histological Changes in the Diminished Nodes as a Result of Several Injections. Necrotic, cheesy foci appeared here and there in the nodes, at the peripheries of which were many giant cells containing several nuclei. The leprosy bacilli had collected in places; often

they had disintegrated into granular masses or had formed a diffuse and hemogeneous swelling. They were usually greatly reduced in number.

TABLE I.—ANATOMICAL FINDINGS IN ANIMALS.

No. of animal.	Lymph glands.	Fatty tissue of peritoneum.	Liver.	Lung.	Result.
1	+	+	+	−	Slight change.
2	+	..	+	+ ?	Slight change.
3	..	+	..	+	Marked change.
4	+	..	−	−	Very slight change.
5 control	+	..	++	++	Marked change.

TABLE II.

No. of guinea-pig.	Body weight.	Date of injection of tubercle bacilli.	Date of injection and dose of solution.		Death.
		1 mg.	First time.	Second time.	
A	95 gr.	May 26	June 6 0.05	....	June 10; accidental.
B	105 "	May 26	June 6 0.05	....	June 10; accidental.
C	95 "	May 26	June 6 0.05	....	June 10; accidental.
D	95 "	May 26	June 6 0.05	....	June 8; died.
E	125 "	May 26	May 26 0.05	June 6 0.05	June 10; accidental.
F	130 "	May 26	May 26 0.05	June 6 0.05	June 10; accidental.
G	100 "	May 26	Control	....	June 10; accidental.
H	105 "	May 26	Control	....	June 10; accidental.
I	105 "	May 26	Control	....	June 10; accidental.
K	110 "	May 26	Control	....	June 7; died.
L	120 "	May 26	Control	....	June 9; died.

TABLE III.

No. of animal.	Macroscopic findings.				Microscopic findings and number of bacilli.					Result.
	Fatty tissue of peritoneum.	Spleen.	Liver.	Lung.	Lymph gland.	Fatty tissue of peritoneum.	Spleen.	Liver.	Lung.	
A	++	+	++	−	+	++	..	....	..	++
C	+++	+	+	−	−	+	..	+ ?	−	++
D	+++	..	....	+ ?	−	++	..	....	?	++
E	+++	++	+	+	..	++	+	++	?	++
F	+++	++	?	?	−	+ No bacilli	..	+ No bacilli	..	++
G Control	+++	++	+	+	++	+++	..	++	..	+++
K Control	+++	?	+	+ ?	+	+++	−	+++	+	+++
L Control	+++	++	+++	+++	..	++	..	++	+	+++

ANIMAL EXPERIMENTATION WITH THE THERAPEUTIC AGENT IN TUBERCULOSIS. *Series I.* Tubercle bacilli were injected in doses

TABLE IV.—SERIES III.

No. of guinea-pig.	Body weight.	Date of injection of tubercle bacilli. 1 mg.	Dose of injection, 0.1% solution.								Body weight.			Deaths.
			June 11	July 19	July 26	Aug. 6	Aug. 16	Aug. 27	Sept. 7	Sept. 17	July 13	July 26	Sept. 17	
1	335	June 11	0.5	0.15	0.2	0.15	0.15	0.12	0.1	0.1	340	345	390	June 20; killed. Weight 400.
2	210	"	0.5	0.1	0.2	..	..	..	..	..	275	260	..	July 30; died.
3	360	"	0.5	0.5	0.2	0.15	0.15	0.1	0.1	0.1	315	315	315	September 20; killed. Weight 245 (scabies).
4 Control	395	"	..	..	..	..	..	..	..	..	390	370	..	August 6; died. Weight 300.

The tubercle bacilli were injected intraperitoneally and the agent intravenously.

of 1 mg. into the livers of five rabbits and followed by the intravenous injection of 2 to 4 cm. of a 0.1 per cent. aqueous solution of potassium cuprocyanide. One rabbit which did not receive the injection was retained as a control. The animals were killed and examined on the twenty-third day after injection.

The simultaneous injection of the agent and of the tubercle bacilli seems to produce an inhibition in the distribution and an increase of the tubercle bacilli.

Series II. The tubercle bacilli were injected intraperitoneally and the therapeutic solution intravenously. This series of animals was attacked and strangled by weasels on the evening of June 10. The next morning five animals (A, C, E, F and G) were found in a condition which made examination impossible. Animals B, H and I were lost.

TABLE V.—POSTMORTEM EXAMINATION.

No. of animal	Macroscopic findings.					Microscopic findings and number of bacilli.					Result.
	Fatty tissue of peritoneum.	Spleen.	Liver.	Lung.	Lymph gland.	Fatty tissue of peritoneum.	Spleen.	Liver.	Lung.	Lymph gland.	
1	−	−	−	−	−	−	−	..	..	..	−
2	..	+?	+	−	+	..	+? bacilli	+? bacilli	+	+?	+
3	−	−.	−	+?	−	..	+	+ No bacilli	−	+?	+−
4	+	++	++	++	+	..	..	++	++	..	++

The attempt shows a good effect in tuberculosis. The disease was finally arrested.

Result of Animal Experiments. If a sufficiently large number of tubercle bacilli be injected intraperitoneally into guinea-pigs the animals sicken and succumb in from five to seven weeks. But if the agent is afterward injected intravenously the animals live for a longer time or recover completely. Histological examination of the animals shows that the former tuberculous foci have healed and that the bacilli have entirely disappeared, while the control animals suffer the ordinary pathological tuberculous changes and finally die.

When the injection of tubercle bacilli into the liver of the rabbit is soon after followed by an intravenous injection of the agent an examination after twenty days will show that the spread of the tuberculous foci has become circumscribed and that the bacilli have diminished in number. When tubercle bacilli are injected intraperitoneally into guinea-pigs and the agent injected intravenously soon afterward the animal dies, as a rule, a few hours later, with chills and a high temperature. Under these conditions the tubercle bacilli which are present in the peritoneal fluids are usually found to have decomposed and become granular in character, whereas those found in the body cells have remained unchanged.

TABLE VI.—SERIES IV.

No. of guinea-pig.	Date of bacilli injection.	Body weight.	Dose of injection of 0.1 per cent. solution.					Body weight.				Death.	Remarks.
			Aug. 6	Aug. 16	Aug. 27	Sept. 10	Sept. 17	Aug. 16	Aug. 27	Sept. 7	Sept. 17		
A	July 30	310	0.15	0.15	0.12	..	..	335	290	..	..	Aug. 31; died.	
B	July 30	370	0.15	0.15	0.12	0.1	..	405	400	370	..	Sept. 13; killed	Suffering from scabies.
C	July 30	375	0.15	0.15	0.12	0.1	0.1	405	400	380	340	Sept. 23; died.	Suffering severely from scabies.
D	July 30	280	0.15	0.15	0.12	0.1	0.1	390	450	516	560	....	October 1, weight 590 grams.
E	July 30	260	0.15	0.15	0.12	0.1	..	295	295	285	..	Sept. 13; killed	Suffering from scabies.
F Control	July 30	300	..	..	1	..	..	325	300	..	..	Aug. 31; died	
G Control	July 30	270	..	..	1	..	..	250	..	..	..	Aug. 16; died	
H Control	July 30	260	..	..	1	..	..	260	..	..	..	Aug. 21; died	

Both tubercle bacilli and agent were injected intravenously. The quantity of bacilli was 1 mg. per animal.

TABLE VII.—AUTOPSY EXAMINATIONS.

No. of animal.	Macroscopic findings.					Microscopic findings and number of bacilli.					Result.	Remarks.
	Lymph gland.	Fatty tissue of perito-neum.	Spleen.	Liver.	Lung.	Lymph gland.	Fatty tissue of perito-neum.	Spleen.	Liver.	Lung.		
A	−	−	−	−	++	+	...	+	+	+	+	Bacilli in very small numbers.
B	−	...	−	−	++	+	...	++	++	++	+	
C	−	...	?	+	−	....	....	+	+	+	+	Bacilli in very small numbers.
D	....	....	....	....	...	...	...	...	...	...	....	Quite well.
E	−	...	−	−	−	+	....	....	+	++	+	Rather many bacilli in lungs. Few elsewhere.
F Control	....	++	−	++	+++	....	....	++	++	+++	++	
G Control	++	++	−	−	+++	+	....	....	++	++	++	
H Control	+	++	−	+	+++	+	++	....	+	++	++	

This experiment demonstrates that the agent is efficacious in tuberculosis, finally effecting a cure.

Histological Findings. The tuberculous nodule is enveloped in a thick capsule, resembling connective tissue. The capsule sends out into the nodule numerous bundles of connective tissue, within which may be seen numerous lymph channels; this is undoubtedly a symptom of the resorption of the nodule. The bacilli in the nodule are often taken up by the epithelioid cells of the tissue and undergo morphological changes.

FIG. 1.—Lepra tuberculosa. Yamagata, aged thirty-three years. Before the injection. Date of photograph, May 13, 1915.

FIG. 2.—Same as Fig. 1 after the injection. Date of photograph, October 4, 1915.

RESULTS OF TREATMENT IN TUBERCULOSIS PATIENTS. A few days after the injection the lung symptoms become aggravated, the quantity of sputum raised is increased, a rise of temperature of about 1° frequently occurs and in many cases the patient feels weak and tired for from two to four days. Then conditions usually show marked improvement, the temperature falling gradually and the appetite being restored.

For three to six days after injection, hemorrhages may be frequent. The sputum is greatly reduced in quantity, even in severe cases, but frequently contains large numbers of bacilli for a long period. According to my experience the bacilli do not wholly disappear from

the sputum until ten to twenty injections have been administered. Patients in the first and second stages of the disease often feel well after five to ten injections. In such cases it is difficult to find the bacilli.

FIG. 3.—Lepra tuberculosa. Tsuchida, aged forty-three years. Before the injection. Date of photograph, May 13, 1915.

FIG. 4.—Same as Fig. 3 after the injection. Date of photograph, October 4, 1915.

Of the numerous cases of tuberculosis treated the results in 51 cases are tabulated below: Of these, 15 were in the first stage (apical catarrh), 28 in the second stage (infiltration) and 8 in the third stage (formation of cavities).

	Cases.
Marked improvement	5
Moderate improvement	19
Slight improvement	9
No improvement or aggravation of certain symptoms and improvement of others	6
Uncertain	11
Exacerbation	1
Total	51

A certain proportion of favorable results were also obtained in the case of other forms of tuberculosis.

Unfavorable Effects. In from 2 to 4 per cent. of patients there were chills and a rise of temperature several hours after injection. These symptoms continued for several hours and must undoubtedly be attributed to the inferior quality of the agent used in the particular cases or to an impure solution. In cases complicated with beriberi the agent may have an unfavorable effect. My limited experience, however, does not permit of any definite statement on this point.

FIG. 5.—Lepra tuberculosa. Nagai, aged fifty-one years. Before the injection. Date of photograph, May 13, 1915.

FIG. 6.—Same as Fig. 5 after the injection. Date of photograph, October 4, 1915.

SUMMARY. 1. Potassium cuprocyanide when injected intravenously has an extremely beneficial effect in leprosy. It is probable that a cure might be effected if the treatment were continued for from six months to a year.

2. A completely therapeutic effect in tuberculosis in animals has been demonstrated. The animals which received intravenous injections of potassium cuprocyanide lived longer than those which had no treatment. After eight to ten injections the animals were completely cured.

3. Potassium cuprocyanide obviously had a favorable effect on tuberculosis in man, including the pulmonary form.

STATUS LYMPHATICUS.

By Douglas Symmers, M.D.,

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(From the Pathological Laboratories of Bellevue and Allied Hospitals.)

The association of sudden death with enlargement of the thymus gland was noted by Bichat early in the eighteenth century, but it remained for Paltauf and others of the Vienna school to show that persistence of the thymus in these circumstances is but one of a combination of hereditary anatomical imperfections occurring in the same body, constituting the condition which is now universally known under the somewhat ponderous and withal inadequate designation of status thymicolymphaticus, or, more simply, as status lymphaticus. Commencing in 1905, Dr. Charles Norris, some time director of laboratories at Bellevue Hospital, made a series of observations on certain peculiarities of configuration in status lymphaticus and called attention to their importance in the clinical detection of the condition. In addition, he pointed out the frequent association of status lymphaticus and certain lesions of the ductless glands, including exophthalmic goitre, Addison's disease, acromegaly and the like, together with its occurrence in suicides and others of unstable emotional qualities. In 1909 Dr. Norris addressed a letter to Professor Edmund von Neusser, of Vienna, directing his attention to the peculiarities of configuration by which status lymphaticus is characterized. Two years later von Neusser published a paper on "The Diagnosis of Status Lymphaticus,"[1] in which he made graceful acknowledgment of his indebtedness to Norris for the diagnostic criteria upon which his paper was founded. In the meantime Norris had read a paper on the same subject before the American Association of Pathologists and Bacteriologists, in Boston, in 1909, in which he made his observations a matter of public knowledge, and in the same year his paper was abstracted at length and published in Volume III of Johnson's *Surgical Diagnosis*.[2] In view of these facts it seems that, in simple fairness, the credit for establishing the clinical signs of status lymphaticus should be bestowed not upon the continental clinician but upon the American pathologist whose astute observations first brought them

[1] von Neusser: Ausgewahlte d. klin. Symptomat. u. Diag., Wien, 1911, p. 197.

[2] Johnson: Surgical Diagnosis, New York, 1910, iii, 704. This volume, although published under the imprint of 1910, was really released in 1909, the copy on file at the New York Academy of Medicine bearing the date of receipt of November 17, 1909.

to light in company with other facts of importance in the same connection, who, frankly and in good faith, submitted them for criticism by a former teacher, and was rewarded by having them incorporated in a paper which has since become a celebrated document in the archives of clinical medicine.

Definition of Status Lymphaticus. Status lymphaticus may be defined as a combination of hereditary constitutional anomalies, entering into which are certain peculiarities of configuration, with preservation or even hyperplasia of the thymus gland at an age when involution is to be expected, hyperplasia of the lymphoid cells in the lymph nodes, spleen, intestine and elsewhere, hypoplasia of the cardiovascular system, developmental deficiencies in the genitalia, and, incidentally, visceral defects of uncertain occurrence and irregular distribution. The condition sometimes is terminated by sudden death, usually in children, but occasionally in young adults.

Status lymphaticus as such is compatible with life; in fact, many subjects not only attain maturity but survive those involutional changes in the lymphoid tissues which, when completed, deprive the condition of certain of its dangers. It is nevertheless a menace, and for at least two reasons: (1) Because it is attended by instability of the lymphoid tissues, providing a mechanism which, when it is once set in motion, is capable of so sensitizing the body as to produce anaphylactic phenomena varying in intensity from simple same irritability of the lymphoid tissues is apparently responsible urticarial rashes to convulsive seizures or sudden death. The for lowering the threshold of infection, particularly those infections which gain entrance through the pharyngeal and faucial tonsils and the intestinal tract. (2) It is a menace because it is attended by defective development of the muscular coat of the arteries, thus rendering them incapable of withstanding changes in blood-pressure which, in ordinary circumstances, are lightly borne.

Clinical Aspects of Status Lymphaticus. Clinical interest in status lymphaticus seems to be focussed almost exclusively on the fact that life may be terminated abruptly on apparently trivial provocation. As a matter of truth, sudden death in status lymphaticus is a tragedy comparatively rarely enacted, but when it does occur the astonishing rapidity of the blow and the unexpected circumstances in which it is delivered are exceedingly impressive. In addition, status lymphaticus touches certain clinical problems of practical value which, however, appear to have been almost completely submerged in the contemplation of spectacular death. It will be the purpose of this paper not so much to emphasize the occurrence of sudden death in status lymphaticus as to impress still further the signs by which the condition may be detected in the living patient, the suggestive frequency with which it is asso-

ciated with various acute infections, with certain disturbances of the nervous system and of the ductless glands, with the occurrence of cerebral hemorrhage in the young, and, finally, its participation in the pathology of caisson disease.

Clinical Signs.—In the clinical conglomerate of scrofula the elder Gross long ago recognized the angelic child, in whom he pointed out the existence of a so-called lymphatic constitution and postulated a connection between it and an unusual susceptibility to tuberculosis, particularly of the bones, joints and lymph nodes. It is now known that children of this type are of the category of status lymphaticus. The angelic child may be described as delicately molded but beautifully proportioned, blue eyed or brown, with long lashes, finely chiselled features, transparent cheeks and rapid mutations in coloring, thin lips, smooth skin and silk-like hair, shapely limbs and quick, graceful movements, narrow waisted, mentally alert, often precocious—a thing of beauty, but lacking in the full promise of life. Such children are not even reasonably assured of maturity but are liable to be eliminated by sudden death or by tuberculosis, cerebrospinal meningitis or other infection. Still other children, with the stigmata of status lymphaticus, are physically and mentally sluggish, coarse featured and sometimes rachitic, but even in these the skin may be fine and the limbs shapely.

After puberty the clinical recognition of subjects of status lymphaticus is even more easily accomplished. In addition to the delicate texture of the skin, which may be velvety to the touch, dead white or faintly cream-colored, sometimes lusterless or paste-like, but rarely muddy, at other times swept by a faint sheen, and the well-nourished, often muscular, finely proportioned body, with its gracefully outlined arms, rotund and arching thighs and slender waist, it is found that in the male the pubic hairs assume the distribution of the female—that is to say, they are sharply defined in a transverse direction and do not tend to grow toward the umbilicus, while the penis is often small and the glans acorn-shaped. The facial and axillary hairs are scantily developed and the thoracic hairs are few in number or totally absent. An exception to this statement, however, is to be noted in certain subjects of status lymphaticus born along the shores of the Mediterranean, in whom the growth of hair may be abundant on both the face and trunk and of normal distribution, and in Orientals, many of whom, according to Crowell,[3] are normally bereft of beard, mustache, axillary and thoracic hair as well as of hair on the extremities. In the female the recognition of status lymphaticus by inspection of the body is rather more difficult, but the diagnosis may be made with relative assurance by the

[3] Phillipine Jour. Science, 1913, No. 2, viii, 77

unusually delicate texture of the skin, by accentuation of the graceful outlines of the body and by the presence of small axillary pads with the scanty growth of hair upon them. In very young children the presence of enlarged tonsils, adenoid vegetations in the nasopharynx and increase in the size and number of the follicles at the base of the tongue may or may not deserve attention as contributing factors in the diagnosis. The converse is imperative, however, that the diagnosis of status lymphaticus be made in those children in whom surgical removal of adenoids is contemplated. In children who have reached or passed the age of puberty, preservation of these enlarged lymphoid structures, together with palpable cervical and other superficial lymph nodes, assumes a place of slightly more significance, but, even at best, it is not a great aid to diagnosis, which, in most instances, may be established without taking these factors into consideration at all.

As age advances the configuration of the body in status lymphaticus may change, partly on account of muscular attrition, but largely because of alterations in the subcutaneous fat. As a rule, however, the conformation is retained to an extent sufficient to combine with the other external features to facilitate diagnosis, and even profound emaciation does not of necessity interfere.

Incidence of Status Lymphaticus. In Bellevue Hospital, in the past twelve years, 457 cases of status lymphaticus were encountered among 5652 autopsies (8 per cent.). In the first 4000 autopsies there were 249 cases. These have been analyzed, statistically and otherwise, and form the basis of this paper.

Sex.—Status lymphaticus was encountered 212 times in males and 37 times in females, which is in the proportion of about 6 to 1.

Age.

Under 1 year	22
1 to 10 years	10
11 to 20 "	20
21 to 30 "	62
31 to 40 "	57
41 to 50 "	41
51 to 60 "	19
Over 60 "	11

Race.—Of the 249 cases 25 occurred in negroes. In this race status lymphaticus, more commonly than in the white, is associated with a degree of muscular development which often is magnificent, the individual muscles standing out as streaming ridges beneath a skin almost as smooth as porcelain.

Of the 224 whites there were 40 Irish, 45 Germans, 7 Hungarians, 20 Italians, 5 Russians, 12 Poles, 3 French, 32 Swedes and 7 Syrians, and 52 in whom the nationality was not recorded. Crowell[4] has

[4] Loc cit.

encountered status lymphaticus among the Philippinos and other Orientals, and Whitmore[5] among the races of British India, so that its geographical distribution is wide.

PATHOLOGY. The anatomical variations in status lymphaticus include of course those external features of configuration and development which have been enumerated, but, in addition, there are changes in other parts that are of importance. These may be classified and described accordingly as they involve (*a*) the lymphoid tissues, (*b*) the cardiovascular apparatus, (*c*) the genitalia and (*d*) under the heading of incidental anomalies of development.

Anatomical Types. In our autopsy protocols we are accustomed to describe two anatomical types depending upon the condition of the lymphoid tissues—status lymphaticus and recessive status lymphaticus. The former is associated with unusually well-developed changes in the lymphoid tissues and occurs at an age when these tissues are naturally flourishing. The recessive type is marked by atrophic changes in the lymphoid structures, varying in extent according to the time of involution, the configuration remaining the same except insofar as it may be modified by the waste of disease or age. Of the 249 cases there were 118 instances of status lymphaticus, 89 cases of recessive status lymphaticus and 42 cases in which the lymphoid tissues were in places hyperplastic, in other places atrophic, in other words, border-line examples, which, however, were tending in the direction of regression.

(*a*) THE LYMPHOID TISSUES. Of the 118 cases of well-developed status lymphaticus the thymus gland was hyperplastic in every instance. The weight of the gland was recorded in 66 cases. The youngest subject was a child of eight hours whose thymus weighed 70 grams and in whom death occurred suddenly, the oldest was an acromegalic individual, aged thirty-eight years, in whom the thymus also weighed 70 grams and in whom death was due to an intercurrent affection. The average weight of the thymus gland, grouped according to years, is shown in the following table:

Age.	Average weight, grams.	Number of cases.
Under 1 year	25.0	13
1 to 5 years	18.0	14
6 to 10 "	24.0	5
11 to 15 "	22.0	5
16 to 20 "	23.0	9
21 to 30 "	27.8	17
31 to 40 "	33.8	3

In the 89 cases of recessive status lymphaticus the thymus was weighable in 19 cases only. The average weights, grouped according to years, are shown in the following table:

[5] Lancet, 1911, clxxxi, 752.

Age.	Average weight, grams.	Number of cases.
18 to 25 years	17.4	6
26 to 35 "	22.0	9
36 to 42 "	15.4	4

In the remaining 70 cases of recessive status lymphaticus the thymus was practically invisible to the naked eye and its position was occupied by a pad of fat or by fat and scattered glandular remnants, the whole corresponding, in a general way, to the normal outlines of the gland.

Sudden death in subjects of status lymphaticus has often been ascribed to pressure of the enlarged thymus upon the trachea. At Bellevue Hospital we have not been able to implicate the thymus as a mechanical factor in the production of death, the anatomical signs of tracheal compression and of death from suffocation never having been found, although sought. In this connection the figures above quoted are significant in that the heaviest thymus—namely, a gland of 70 grams—was greatly below the weight necessary for compressing the trachea, as shown by experiment, which, according to Tamassia,[6] is at least 180 grams.

In the 118 cases of well-developed status lymphaticus the faucial tonsils were hyperplastic 61 times (51 per cent.), the lingual tonsils 58 times (49 per cent.) and the pharyngeal tonsils 45 times (37 per cent.). Peyer's patches and the solitary follicles were each hyperplastic in 105 cases (88 per cent.), sometimes in combination, at other times independently.

The spleen was described as small or normal in size in 68 cases (70 per cent.). In 26 cases the spleen was enlarged, but in all of them contributing factors were found to account for the enlargement, such as cirrhosis of the liver, sepsis, enteric fever, etc. This observation is of interest in connection with the statement of von Neusser that enlargement of the spleen is a factor in the diagnosis of status lymphaticus in the living patient. In our experience enlargement of the spleen is not a part of the pathology of status lymphaticus and should not be taken into clinical account except as it has to do with associated conditions.

The splenic lymphoid follicles were hyperplastic in 105 cases (88 per cent.).

The mesenteric lymph nodes were enlarged in 7 cases only, the axillary nodes 11 times, the inguinal nodes 12 times, the cervical nodes 15 times and the peribronchial nodes 5 times—in other words, changes in these situations are, for all practical purposes, negligible.

The figures referable to hyperplasia of the lymph nodes and intestinal follicles in recessive status lymphaticus form an interest-

[6] Quoted by Blumer, vide loc. cit.

ing contrast to those quoted. Thus in 89 cases of recessive status lymphaticus the faucial tonsils were enlarged 25 times (28 per cent.), the lingual tonsils 32 times (36 per cent.), the pharyngeal tonsils 19 times (21 per cent.). Peyer's patches were enlarged 11 times (12 per cent.) and the solitary follicles 19 times (21 per cent.).

In the 89 cases of recessive status lymphaticus the spleen was described as normal or small in 52 (71 per cent.). The spleen was enlarged in 21 cases, in 17 of which enlargement was due to some accompanying lesion, such as chronic valvular disease, cirrhosis of the liver, etc.

The splenic follicles were hyperplastic in 37 cases (41 per cent.).

HISTOLOGY.—The histology of the thymus gland in most subjects of well-developed status lymphaticus presents nothing worthy of note other than hyperplasia of the cortical lymphoid follicles, but in many cases this is extreme. In other cases it is to be observed that there are large blood sinuses in the thymus and that they contain greatly increased numbers of lymphocytes. Whether this has any connection with the lymphocytosis which is sometimes encountered in the peripheral blood is a question to which, unfortunately, we are unable to give a definite reply. In Graves's disease, however, it is known that lymphocytosis is a frequent occurrence and that the thymus is hyperplastic often to an extraordinary degree. Shridde[7] and others have pointed out that those patients in whom there is a lymphocytosis of 40 per cent. or over are dangerous operative risks and are liable to sudden death, which is in keeping with the known frequency of sudden death in Graves's disease in patients with persistent and hyperplastic thymi. That the lymphocytosis of Graves's disease is due to expulsion of thymic lymphoid cells into the circulation seems reasonably assured in view of the rich numbers of lymphocytes commonly to be found in the bloodvessels of the persistent and hyperplastic thymus. No doubt the hyperplastic lymph nodes also contribute their share of lymphocytes. In any event the number of lymphocytes in the circulating blood may be accepted as a more or less reliable index of the degree of lymphoid hyperplasia and should be taken into consideration in estimating operative risks in subjects of status lymphaticus.

Necrotic Changes in the Lymph Nodes. Microscopic examination of the lymph nodes in status lymphaticus shows the presence of vastly increased numbers of lymphocytes, the hyperplasia tending to bring about rearrangement of the architecture of the node by increase in the size and number of the so-called germinal follicles, and by overflow of cells into the tissue spaces and sometimes into the endothelial sinuses.

[7] Deutsch. med. Wchnschr., 1911, xxiii, 1103.

In a considerable majority of all cases of well-developed status lymphaticus, but especially often in subjects who have met death suddenly and in response to apparently trivial provocation, the lymph nodes show a peculiar and characteristic change in the form of necrosis of the germinal areas attended by extensive disintegration of cells and the discharge of nuclear dust into the intercellular spaces. In still other cases of status lymphaticus, particularly in subjects who have passed the age of puberty, and in recessive status lymphaticus, the germinal follicles often show almost complete replacement by whorl-like collections of spindle cells representing, apparently, connective-tissue elements. Lying among the spindle cells are to be made out rather large polyhedral forms resembling degenerate cells of the type of large lymphocytes. The cytoplasm of both the spindle and polyhedral cells stains pink with eosin, so that the follicle stands out in contrast to the deep blue of the small lymphocytes in the immediate vicinity. The changes in question were originally described by Lartigau,[8] later by Blumer,[9] and, in this laboratory, we do not hesitate to make the microscopic diagnosis of status lymphaticus from these findings alone. We have yet to observe them in any condition other than status lymphaticus. They occur not only in follicles of the lymph nodes themselves but in those of the intestine, the lingual, faucial and pharyngeal tonsils, in the follicles of the spleen and, on at least one occasion, I have seen them in the hyperplastic follicles in the interstitial tissues of the thyroid gland from a case of Graves's disease.

The histological changes in the several lymphoid depots in the older cases of status lymphaticus, including, of course, the recessive type, reveal simple diminution in the numbers of lymphoid cells usually with but sometimes without the presence of necrotic, degenerative or fibrotic alterations in the germinal follicles.

The histology and distribution of the lymphoid tissues are, I believe, of fundamental importance in the interpretation of anaphylaxis as a cause of sudden death and of certain convulsive phenomena occurring in subjects of status lymphaticus.[10] Thus, the lymphoid tissues are most abundantly developed in youth and early adolescence, tending to disappear as age advances, which is in keeping with the observation that in status lymphaticus the danger of sudden death is greatest during that period of life in which the lymphoid tissues are most flourishing and is almost unknown in the recessive stage. It is likewise significant that in status lymphaticus those lymphoid tissues which display the highest degree of hyperplasia are to be found in the mucous membrane of the gastro-intestinal tract, where, of all the lymphoid structures, they are the ones most actively

[8] Ann. Surg., 1902, xxxv, 745.
[9] Johns Hopkins Hosp Bull., 1903, xiv, 270.
[10] Symmers: Am. Jour. Dis. Children, 1917, xiv, 463.

engaged in the process of filtration, in the course of which they are constantly subjected to the destructive action of a great variety of toxic substances, both chemical and bacterial. In children suddenly dead with all the physical attributes of status lymphaticus, microscopic examination of the lymphoid tissues throughout the body shows, with rare exceptions, myriads of necroses in the germinal follicles of the sort already described. These changes indicate, I believe, that sudden death in status lymphaticus is connected with the release of nucleoproteids formed as a result of destruction of innumerable germinal follicles. It is scarcely conceivable, however, that death is directly traceable to the toxemia produced by sudden and simultaneous destruction of a large number of follicles, as maintained by Blumer,[11] since the interval between injury and death is far too short, in the majority of cases, to permit so many necrotic lesions to occur throughout such a wide distribution. It is more probable, I think, that death is of the nature of an anaphylactic reaction, sensitization being expressed in structural terms by the necrotic germinal follicles, and, chemically, by the release of nucleoproteids which, although not strictly foreign, are none the less pathological, and are comparable, in a toxicological sense, to alien products. Previous to the expiration of the so-called anaphylactic incubation period the lymph nodes are again subjected to the action of destructive substances which serve to bring about still further disintegration of germinal nuclei, thus providing the requisite quantity of specific proteid to complete the anaphylactic cycle. The destructive substances in question may be introduced in the form of antitoxins hypodermically injected, or as vaccines applied by scarification or otherwise, or as substances which have escaped destruction or modification by the hyperplastic lymphoid follicles in the intestinal tract, or which have been manufactured in the process of shock induced even by such simple procedures as the prick of a needle, sudden immersion in cold water and similar events.

That acute necroses may occur in irregular showers is shown by the presence of all stages of both the necrotic and reparative processes in the same lymph node or in different nodes in the same body. This fact is of moment in that the anaphylactic reactivity of the body is determined by the number of acute necrotic lesions in the germinal follicles, or, in other words, the anaphylactic incubation period in man, as in experimental animals, varies with the initial dose of the sensitizing proteid. For example, in guinea-pigs injected with small amounts of horse serum from twelve to fourteen days suffice for sensitization. With larger doses, however, the interval may be extended to weeks or months. In subjects of status lymphaticus it is naturally to be expected that early sensiti-

[11] Vide loc. cit.

zation follows a small shower of necroses and that larger showers are succeeded by a longer period of incubation, the reactive ranges thus varying within wide limits, both in the matter of time and intensity. At one moment the tissues are exquisitely tuned and await only the receipt of a sufficient quantity of specific protein to react violently, even to the extent of sudden death, while at another moment events are so timed that the same quantity of specific protein exerts no such effect, a fact which tends to explain why certain subjects of status lymphaticus survive surgical and other procedures which, in others, are attended by disaster. In this instance it is apparently a question of anaphylactic reactivity dependent upon the number of acute necrotic lesions in the lymph nodes and upon the interval which has elapsed since their inception.

Idiopathic Epilepsy. The theory of anaphylactic shock is also applicable, I believe, to the convulsive disorders of certain subjects of idiopathic epilepsy, most of whom, according to Karpas, present the typical configuration of status lymphaticus. It impresses me as a matter of extreme significance that the victims of idiopathic epilepsy may cease to have convulsive seizures at an age when involution of the thymus gland is to be expected or has actually taken place. In the case of a negro, aged twenty-six years, who recently came to autopsy at Bellevue Hospital, there was a history of epileptic seizures attended by biting of the tongue that occurred with frequency throughout early life, but which diminished at about the twelfth year and disappeared by the fourteenth. Death was due to dilatation of the heart, and autopsy revealed the characteristic configuration of status lymphaticus, partial atrophy and fatty replacement of the thymus gland, and irregularly distributed atrophic changes in the lymphoid tissues elsewhere.

If it is true that idiopathic epilepsy and status lymphaticus stand in relationship to one another the suggestion appears to be not out of place that subjects of idiopathic epilepsy might readily derive benefit from exposure of the thymus and spleen, possibly the intestines, to the *x*-rays, since it is known that radiation discourages proliferation of lymphoid tissues and brings about atrophy of those already present.

(*b*) The Cardiovascular System: Of the 249 cases of status lymphaticus and recessive status lymphaticus encountered among the first 4000 autopsies at Bellevue Hospital the heart was described as small or normal in size in 127 (51 per cent.). In 46 cases the heart was enlarged, due, in every instance, to inherent valvular disease or to chronic interstitial nephritis, emphysema and similar causes.

Of the 249 cases the aorta was described as hypoplastic in 101 cases (40.5 per cent.). In 71 of these cases hypoplasia was determined by actual measurement of the relative width of the pulmo-

nary artery and the aorta. In 8 cases the measurements were the same. In the remaining 63 cases the average width of the pulmonary artery and aorta was 6.6 cm. and 5.7 cm. as opposed to the normal measurements of 6.5 to 7 cm. and 7 to 7.5 cm. In 78 cases (31 per cent.) the elasticity of the aorta was increased and in 66 cases (26.5 per cent) the vessel was described as unusually thin.

Status Lymphaticus and Aortitis: It is worthy of remark that in 249 cases of status lymphaticus there were 37 instances (about 15 per cent.) in which anatomical changes due to syphilis were detected in various parts a slightly higher percentage than that usually accredited to subjects coming to autopsy in Bellevue Hospital, 6.5 per cent. in a series of 314 cases[12] of late acquired syphilis, having shown syphilitic lesions. Of the 37 cases of syphilis associated with status lymphaticus the aorta was the seat of syphilitic lesions in 15 instances (40 per cent.). In 4 cases the aorta from commencement to bifurcation was the seat of syphilitic aortitis, in 9 cases the changes were advanced but were limited to the arch, in 1 case there was syphilitic aortitis of the arch and thoracic aorta and in 1 case a small aneurysm of the sinus of Valsalva was imposed upon a limited syphilitic aortitis of the ascending aorta. In one of these cases syphilitic aortitis was associated with extensive chronic interstitial myocarditis and in another multiple gummata were present in the heart muscle. It appears therefore that syphilitic aortitis which, in the ordinary course of events, is present in somewhat over 55 per cent. of all syphilitic subjects investigated postmortem at Bellevue Hospital is neither more nor less frequent or severe in status lymphaticus than otherwise and that the thinness and increased elasticity of the aorta in status lymphaticus is not of great moment so far as increased susceptibility to syphilitic aortitis and aneurysmal dilatation are concerned. Moreover, it is probable that the increased elasticity of the vessel is a detriment to those mechanical factors which favor aneurysmal dilatation.

Acute Gelatinous Aortitis: In the 249 cases of status lymphaticus there were 15 cases of the acute gelatinous aortitis described by the French. This lesion is characterized by swelling, opacity and stickiness of the intima, attended, microscopically, by enlargement and vacuolation of the endothelial cells. In our cases it was associated with croupous pneumonia 8 times, bronchopneumonia 4 times, suppurative pericarditis, sepsis and acute miliary tuberculosis once each. The lesion, so far as I am aware, has no practical significance.

Status Lymphaticus and Cerebral Hemorrhage in the Young: In status lymphaticus the cerebral vessels, particularly the arteries entering into the formation of the circle of Willis and the branches

[12] Symmers: Jour. Am. Med. Assn., 1916, lxvi, 1457.

which emerge therefrom, are often small in caliber and extremely thin and delicate.[13] As seen at autopsy the larger vessels at the base, for example, are collapsed, one wall lying against the other and, when removed from the body and viewed by transmitted light, they are easily translucent. Upon microscopic examination these vessels show simple hypoplastic alterations, the deficiency being most marked in the muscular coat, which is distinctly less developed than in normal circumstances. The exact incidence of these changes in status lymphaticus has not been determined but the association has been noted with such frequency as to leave no doubt that the two are companion manifestations of one and the same underlying developmental defect.

Hypoplasia of the cerebral vessels in subjects of status lymphaticus is of profound importance from the stand-point of sudden death, not only sudden death ensuing spontaneously, but in subjects who have been exposed to a degree of injury which, in normal individuals, would be regarded as insignificant. In the latter group of cases its medicolegal application cannot be overestimated. In the experience of Dr. Otto H. Schultze, the pathologist to the district attorney's office in the city of New York and in our own postmortem work at Bellevue Hospital, cerebral hemorrhage in young, non-syphilitic subjects of status lymphaticus occurs a number of times in the course of every year, and is due to rupture of hypoplastic cerebral arteries occurring spontaneously or upon the receipt of apparently trivial traumatism or under the influence of physical strain or intense excitement. In such subjects, therefore, any influence which causes sudden increase in intracranial blood-pressure may be disastrous, such as heavy lifting, straining at stool, the tension of argument, fighting, etc.

In the 249 cases of status lymphaticus, sudden death due to spontaneous rupture of a hypoplastic cerebral artery occurred 7 times (3 times in men and 4 times in women), all of them under thirty years of age, none of them presenting syphilitic or precocious arteriosclerotic changes in the vessels of the brain or elsewhere. The clinical symptoms were those of cerebral hemorrhage and death occurred rapidly. In one of these cases the patient, a clerk, aged twenty-eight years, walked into the hospital complaining of headache of two or three days' duration, weakness and nausea. Death occurred a few hours after admission. In a second case the patient, an elocutionist, was apparently perfectly well until the morning of admission, when she suddenly became unconscious and died with signs of complete left-sided hemiplegia. In a third case the patient, a factory girl, aged nineteen years, upon arriving home one night suddenly fell in the doorway, shrieked loudly, and the

[13] Wiesner: Verh. d. deutsch. path. Gesellsch., 13 Tagung, 1909.

ambulance surgeon who went to her relief found complete paralysis of the left side of the body. Death occurred the following day. In these as in the remaining 4 cases autopsy revealed rupture of hypoplastic cerebral bloodvessels, hemorrhage occurring in the pons and medulla, the ventricles, the lenticular and caudate nucleus, the lenticular nucleus, the cerebellum, the temporal and right occipital lobe respectively. In still other instances, however, hemorrhage is confined to the pia arachnoid.

In the past year Dr. Schultze tells me that in one of his cases a boy fell dead while engaged in a fisticuff, and another, a young woman, died while straining at stool. It is quite apparent, therefore, that the problem abounds in medicolegal possibilities and that the clinical or postmortem recognition of status lymphaticus and its not infrequent association with this form of sudden death is of paramount importance, since failure properly to appreciate the connection between the two may jeopardize a man's life or liberty.

Cerebral hemorrhage in the young is oftenest ascribed to rupture of miliary aneurysms, which are usually regarded as of syphilitic origin. In many cases their syphilitic nature is apparent. In other instances, however, they appear to arise purely on the basis of congenitally hypoplastic bloodvessels. In the syphilitic cases aneurysmal dilatation occurs at a point in the muscular coat or elsewhere marked by the presence of minute gummata, with or without central necrosis, thus providing a field of diminished resistance. In 5000 autopsies at Bellevue Hospital miliary aneurysms of syphilitic origin occurred 7 times. On the other hand, there were 9 cases in which miliary aneurysms occurred in congenitally hypoplastic bloodvessels without the intervention of degenerative or inflammatory changes traceable to syphilis. Four occurred in females, the youngest subject a girl, aged seventeen years, and 5 in males, the oldest subject a man aged sixty-four years. The average age was forty-two years. In all of these cases the vessels at the base of the brain were described as extremely delicate, the walls being translucent and collapsed. In 5 cases the hypoplastic cerebral vessels were encountered in individuals presenting the anatomical changes in the kidney incident to chronic interstitial nephritis. In 2 of these cases there were small sclerotic foci to be made out in the cerebral arteries concerned, thus affording a favorable site for aneurysmal dilatation. In the other 4 cases the hypoplastic vessels were found in subjects of status lymphaticus. One of these exhibited the anatomical signs of chronic interstitial nephritis. The other 3 presented acute vegetative lesions in the heart valves, which, possibly, contributed to aneurysmal dilatation of the cerebral vessels by the discharge of infective emboli and the production of inflammatory lesions at the point of lodgment.

Status Lymphaticus and Caisson Disease: Hypoplasia of the smaller bloodvessels in status lymphaticus is apparently an element

of danger in workers in compressed air, 5 cases of caisson disease having been examined postmortem in Bellevue Hospital in individuals showing the characteristic stigmata. All of them were young, muscular adults. Three presented the configuration of status lymphaticus. In 2 of them the protocols were silent on this score. In all of them the aorta was markedly hypoplastic. In 2 the thymus was described as enlarged, in the other 3 the thymus weighed 27, 35 and 25 grams respectively. In 4 cases the splenic follicles were enlarged. In 1 case the lingual and faucial tonsils and the solitary and agminated follicles in the intestine and the mesenteric nodes were unduly prominent and in 3 cases the intestinal follicles alone were hyperplastic. All of the bodies presented innumerable odorless air bubbles in the vessels of the brain and trunk. From these 5 cases, which represent the sum total of our experience in caisson disease during a period when active tunnelling operations were under way in New York City, it is quite apparent that status lymphaticus constitutes a contra-indication to the acceptance of a workman for duty in an atmosphere of compressed air even though decompression be brought about with scientific exactitude. Just why this should be true is not apparent, but it probably has something to do with defective permeability of congenitally hypoplastic bloodvessels, so that tissues saturated with nitrogen under pressure yield this gas under decompression in such quantities that the blood cannot take it into solution and it circulates as emboli.

Status Lymphaticus and Emotional Instability: Emerson,[14] working in the alcoholic wards at Bellevue Hospital, examined 1000 patients suffering from the effects of attempted suicide and from cocain, morphin, heroin, alcohol and similar habituating drugs. Of this number 220 (22 per cent.) showed most or all of the physical stigmata of status lymphaticus. I have had occasion to note the characteristic configuration of status lymphaticus in sufferers from neurasthenia and in certain primitive races. In the autopsy rooms at Bellevue Hospital, which are utilized by the several coroners' physicians and by Dr. Schultze, of the district attorney's office, for the performance of autopsies in medicolegal cases, it is a matter of almost daily observation that suicides and degenerates, and gunmen and other criminals who have met death by violence, present the characteristic conformation and anatomical changes of status lymphaticus. According to the combined statistics of Bartels[15] and Miloslavich,[16] amounting to 232 cases of suicide, 80.5 per cent showed the signs of status lymphaticus at autopsy. Among epileptics and the insane the condition is common (Karpas).

It is scarcely conceivable that status lymphaticus occurring with such frequency among such a diversity of individuals of unstable

[14] Arch. Int. Med., 1914, xiii, 169; Med. Press, October 15, 1913, p. 418.
[15] Wien. klin. Wchnschr., 1908, lv, 1826.
[16] Virchows Arch., 1912, ccviii, 44.

emotional qualities could be purely accidental. It seems more within reason to assume that congenitally hypoplastic bloodvessels are under indifferent vasomotor control and that this is not without influence upon mental poise.

Status Lymphaticus and Exophthalmic Goitre: The association of status lymphaticus and exophthalmic goitre, while not constant, is common, and is particularly noteworthy in connection with the incidence of status lymphaticus among the emotionally unstable. In 6 cases of exophthalmic goitre investigated postmortem at Bellevue Hospital, signs of status lymphaticus were present in 5, in some better developed than in others. In 3 cases the thymus was enlarged, weighing 45, 64 and 26 grams respectivelly, and in all the configuration was typical and the lymphoid tissues were hyperplastic. In a fourth case the thymus was partially replaced by fat, but glandular remnants were still visible and the follicles in the spleen were numerous and large. In a fifth case the configuration was typical, but the lymphoid tissues had undergone marked regression. It is furthermore interesting to record that, with other pathologists, I have not uncommonly seen hyperplastic follicles in the stroma of the thyroid gland removed from subjects of exophthalmic goitre at operation or autopsy. Capelle[17] collected 60 cases of Graves's disease from the literature. In 44 per cent. the patients died from intercurrent affections, and in all of them the thymus was persistent and hyperplastic. Of those dying of Graves's disease without associated lesions, 82 per cent. presented enlargement of the thymus, while in cases of sudden death following operation for removal of the thyroid the thymus was hyperplastic in all.

It has long been known that derangement of the emotional nervous system, manifested by intense grief or fear, may rapidly be followed by the symptoms of exophthalmic goitre, that exophthalmic goitre frequently is implanted in young women of uncertain emotional balance, sometimes in a family whose genealogy is marred by a history of epilepsy, insanity and kindred disorders, and that a certain proportion of all cases of Graves's disease follows influenza or streptococcal throat infection, either of which is prone to leave its victim mentally perturbed. That Graves's disease not infrequently follows shock has been amply exemplified by the present war, numbers of soldiers exposed to the terrifying vicissitudes of trench life having been invalided with symptoms of Graves's disease varying in intensity from simple tachycardia and muscular tremors to the fully developed picture.[18] It seems not improbable that exophthalmic goitre, in certain subjects of status lymphaticus at least, is the result of disturbances in an already unstable nervous system that have so altered the function of the thyroid gland as

[17] München. med. Wchnschr., 1908, lv, 1826.

[18] Stoney: Lancet, April 8, 1916, p. 777; ibid., White and Hernaman-Johnson, January 8, 1916, p. 78.

permanently to externalize the physical attributes of fear as expressed by protruding eyeballs, irregularity and increased rapidity of the heart's action, muscular tremors, clammy sweats, pallor and the like. In other words, the subject of status lymphaticus, as a result of hereditary anatomical imperfections, appears to be more susceptible to those influences, infective, psychic or otherwise, which precipitate exophthalmic goitre than the indivdual who more nearly approaches the normal. This hypothesis, at all events, is more in consonance with established facts than the extreme view of certain students of the French school who maintain that Graves's disease is the direct result of disturbances in the thymus gland rather than the thyroid, and who have advocated and actually practised thymectomy for its relief. The alternative, as far as I can judge, is to dismiss the association of status lymphaticus and Graves's disease as accidental, and this seems scarcely justified by circumstances.

Chlorosis: It has been pointed out by Virchow that in chlorotic girls the aorta is hypoplastic and the genitalia, notably the uterus, of the infantile type. Not only are these deficiencies common to status lymphaticus in the female, but it is a matter of observation that chlorotic girls almost invariably present a skin of exquisite texture and that the normally graceful outlines of the body are accentuated and the subcutaneous fat well preserved. That the vasomotor system is easily disturbed is shown by frequent changes in color, by the paradoxical association of rosy cheeks with pronounced anemia—the so-called chlorosis rubra—by dermatographia and by a tendency to syncope which is often out of proportion to the severity of anemia, while emotional disturbances are notoriously common. In short, the anatomical signs and the symptoms of chlorosis suggest that this form of anemia is an incidental and fugitive condition in girls with status lymphaticus.

Status Lymphaticus and Acute Infection: There is very little in the literature bearing on the susceptibility of subjects of status lymphaticus to infection. Daut[19] has shown, however, that over 25 per cent. of patients dying of diphtheria present the anatomical changes of status lymphaticus. Elser's[20] observations on epidemic cerebrospinal meningitis lead him to the conclusion that status lymphaticus, occurring in over a quarter of all subjects examined at autopsy, constitutes a predisposing factor in this variety of infection, and, in addition, he noted that the issue is apt to be rapidly fatal in patients of this sort. Blumer[21] has reported a case of tetanus in a boy, aged twelve years, in whom death occurred after an unusually short illness.

In 249 cases of status lymphaticus investigated postmortem at

[19] Jahrbuch. f. Kinderheilk., 1898, xlvii, 141.
[20] Jour. Med. Research, 1905, ix, 89.
[21] Vide loc. cit.

Bellevue Hospital acute infective lesions occurred in 222, or in 88 per cent., distributed thus:

Acute infective endocarditis	51
Croupous pneumonia	36
Epidemic cerebrospinal meningitis	33
Bronchopneumonia	21
Sepsis	15
Acute general miliary tuberculosis	14
Suppurative otitis media	10
Acute miliary tuberculosis of lungs	6
Tuberculous pneumonia	5
Pyonephrosis	5
Enteric fever	5
Pneumococcal meningitis	3
Diphtheria	3
Abscess of lung	3
General peritonitis	3
Empyema	2
Purulent cystitis	1
Purulent tonsillitis	1
Ulcerative colitis	1
Erysipelas	1
Smallpox	1
Abscess of the mouth	1
Abscess of the spleen	1

Status Lymphaticus and Acute Infective Endocarditis. Of the 249 cases of status lymphaticus the heart valves were involved 88 times, but in 37 of these the valvular lesions were chronic and have been excluded from the above list. Of the 37 chronic valvular lesions the youngest occurred in a subject of eight years and the oldest in a man of sixty-two years. The average age was 39.9 years. The aortic valves were alone involved in 9 cases—3 were stenotic lesions and 3 occurred in syphilitic subjects. The mitral valves alone were involved in 12 cases, 5 of them being stenotic lesions. The aortic and mitral valves together were concerned in 10 cases and the aortic mitral and tricuspid together were involved 4 times, the tricuspid valves alone in 2 cases.

Acute infective lesions of the heart valves were superimposed upon chronic sclerotic valvulitis in 26 cases. The youngest subject was a fourteen-year-old boy and the oldest a man, aged forty-five years. The average age was 22.5 years. The aortic valves were alone involved in 5 cases, the mitral valves in 4, the mitral and aortic valves together in 9, the aortic, mitral and tricuspid together in 4 the mitral and tricuspid in 3 and all the valves of the heart in 1.

Acute infective lesions occurring in otherwise apparently healthy valves were encountered 25 times. The youngest subject was aged four and the oldest forty-four years. The average age was 24.4 years. The aortic valves were alone concerned 6 times, the mitral valves 4 times, the aortic and mitral valves 8 times, the aortic, mitral and tricuspid 3 times, the mitral and pulmonary, the mitral, pulmonary and tricuspid, the aortic and tricuspid and the mitral and tricuspid once each. Associated with the lesions enumerated the left

auricle was the seat of vegetative endocarditis twice, the wall of the left ventricle 4 times, and there were vegetations in the arch of the aorta in 3 cases and in the pulmonary artery once.

In 249 cases of status lymphaticus, therefore, there were 88 cases of endocarditis (35.3 per cent.), of which number 51, or 57.8 per cent., were acute. It seems scarcely possible to evade the conclusion that status lymphaticus is a distinct predisposing factor in those infective processes which exert a selective action on the heart valves and in which, in many cases, the provocative microorganism enters the body through the tonsils. Even though the 26 instances of acute infective endocarditis superimposed upon valves already the seat of sclerotic lesions be excluded on the ground that local conditions were propitious for infection, the fact still remains that about 10 per cent. of all subjects of status lymphaticus present acute infective lesions of the heart valves—a point quite worthy of remembrance in dealing with obscure symptoms of infection in patients of this type.

Status Lymphaticus and Epidemic Cerebrospinal Meningitis: In 1906–07 there was an epidemic of cerebrospinal meningitis in New York City and 55 cases were submitted to autopsy at Bellevue Hospital. Of this number 33 (60 per cent.) occurred in young subjects of status lymphaticus. The meningococcus was isolated in every instance. The thymus was described as greatly enlarged in 4 cases, very large in 2 cases, large in 6 cases, persistent in 1 case, and in 7 cases the weights were recorded as 15, 12, 68, 20, 27, 28 and 31 grams respectively. Of the 33 cases it was possible to ascertain the duration of symptoms in 30, and death occurred as shown in the following table:

Number of cases.	Duration of symptoms.
1	1 day
8	2 days
4	3 "
4	4 "
4	5 "
2	8 "
1	11 "
1	13 "
1	17 "
1	20 "
1	21 "
1	(healed) 45 "
1	" 59 "

In 23 of the 30 cases (70 per cent.) death occurred after the lapse of an average interval of 3.4 days, which, of course, is an exceedingly short period of illness. In other words the subject of status lymphaticus is extremely susceptible to infection by the meningococcus and the disease is apt to pursue a remarkably rapid course. Here, again, the hyperplastic lymphoid tissues in the tonsils and nasopharynx are probably remiss in their function as part of the body's filtration plant.

Status Lymphaticus and Enteric Fever: In 6562 autopsies at Bellevue Hospital there were 81 cases of enteric fever, only 5 of which are included in the list of general infections above. Of the total number, 16 (19.7 per cent.) occurred in subjects of status lymphaticus, 12 times in males and 4 times in females. The youngest subject was a boy, aged seventeen years, the oldest a man, aged forty years. The average age was 25.5 years. All of them, with 3 exceptions, were subjects of well-developed status lymphaticus, the remaining 3 cases being of the recessive type. In all of the cases the typhoid bacillus was isolated in pure culture.

Of the 16 cases it was possible to ascertain the duration of illness in 13, dating from the time that the several patients actually took to bed. The duration was as shown in the following table:

Number of cases.	Duration of illness.
1	3 days
1	4 "
1	5 "
1	10 "
2	11 "
1	14 "
1	16 "
1	17 "
1	18 "
2	24 "
1	26 "

The average duration of illness was therefore fourteen days, which for enteric fever is far short of the average expectation in fatal cases.

In the 16 subjects of status lymphaticus dead of enteric fever the reaction of the lymphoid tissues in the intestine varied noticeably. In one type of case the ulcers in the intestine were numerous, large and deep and the non-ulcerated follicles in the vicinity were only moderately hyperplastic. Seven such cases occurred, and of this number 3 were attended by perforation and purulent peritonitis, 2 by ulcers which extended into the musculature and 1 by ulcers which were limited externally by the serosa. In a second type of case the solitary and agminated follicles were greatly increased in size and the ulcerations were superficial, sometimes to such an extent that it was difficult to make them out by the unaided eye. Changes of this type were noted in individuals who had not yet passed the second week, death apparently being due to intense toxemia. In the Bellevue series 7 such cases occurred. In 5 of these cases the solitary follicles and Peyer's patches were markedly hyperplastic and superficially ulcerated. In another case the ileocecal orifice was almost closed by an enormously hyperplastic, congested and superficially ulcerated Peyer's patch, the patches in the ileum just above being enlarged to such an extent that they projected into the lumen as mushroom-like growths, the solitary follicles standing out as tab-like bodies. In another case

the ileocecal Peyer's patch appeared as a polypoid outgrowth and was richly congested and superficially ulcerated. In a third type of case the ulcerated areas displayed signs of healing. Two examples were encountered. In 1 case the ileum showed numerous small ulcers, many of which were surrounded by a whitish zone. In the colon, however, were many large ulcers and an enormous collection of free blood, and no doubt the lesions in the large intestine represented an expression of reinfection. In a second case of this type the small and large intestine showed numerous smooth, plaque like areas of ulceration.

(*c*) THE GENITALIA. In male subjects of status lymphaticus, according to our observations at Bellevue Hospital, the penis is small in about 12 per cent. of all cases, while the glans is pointed or acorn-shaped and small in about 18 per cent. In a considerable number of all cases microscopic examination of the testicles showed the peculiar connective-tissue hyperplasia described by Kyrle[22] as a developmental defect in the testicles of many young subjects. The function of spermatogenesis was apparently active.

In female subjects of status lymphaticus the uterus is hypoplastic in a considerable number of cases.

In view of the fact that the cortex of the suprarenal capsule is embryologically related to the testicle in the male and the ovary in the female it is worthy of note that Norris and Wiesel have pointed out the almost constant occurrence of hypoplasia of the suprarenal cortex in subjects of status lymphaticus.

(*d*) Finally, it is to be mentioned that subjects of status lymphaticus not uncommonly show such peculiarities as supernumerary lobulations in the lungs and similar unimportant although interesting developmental anomalies.

A STUDY OF OCHRONOSIS.

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AN excellent opportunity to observe this rare and obscure disease was recently afforded by a case coming to autopsy. This case was of unusual interest, as it presented a strong clinical resemblance to alcaptonuria. Investigation of the melanotic pigment present led, however, to the diagnosis of ochronosis with melanuria, no direct relation to the alcaptonuric condition being discovered.

In the present article the writer's investigation of the metabolism

[22] Wien. klin. Wchnschr., 1910, No. 45, p. 1583.

of ochronosis is reported.[1] In the first part of the paper are reported the results of the chemical studies, which are applied in the succeeding pages in a discussion of the pathogenesis of ochronosis and the relation of ochronosis to alcaptonuria.

CASE ABSTRACT.—M. K., aged forty years, male. Chief complaints, weakness, stiffness of joints and black discoloration of the urine. Duration of the disease, eighteen months. Examination showed emaciation, bluish pigmentation of the scleræ, aural cartilages and axillæ; arthritis of spine and various larger joints. The patient's cachexia increased after admission, decreasingly smaller amounts of the melanotic urine being passed until death ensued three weeks after admission. Autopsy disclosed intense black pigmentation of the superficial bones, especially the ribs, also the presence of melanotic calculi in the prostate. Histological examination showed the typical pathological changes originally described by Virchow under the name of *ochronosis*, which refers to the yellow color of the pigment granules under the microscope. A prostatic calculus and a rib cartilage were reserved for chemical examination.

Prostatic Calculus. The calculus was rounded in form, about 1 cm. in diameter; after drying in the air it measured about one-half this size. It was brown black in color and consisted of several lobes. It was amorphous throughout. A cavity in the center may have represented the site of a corpus amalaceum. An outer brown-black layer was carefully removed, exposing the coal-black pigment which made up the bulk of the calculus. The latter was used for combustion. Weight of the air-dried concrement was 0.12 gm.

Elementary analysis by courtesy of Dr. P. A. Levene, Rockefeller Institute, New York City: 0.0832 gm. dried in vacuum at 100° gave 0.1572 gm. CO_2 and 0.0392 gm. H_2O. Carbon = 51.52 per cent. Hydrogen = 5.27 per cent. There remained after combustion 0.0062 gm. ash = 7.45 per cent.

Urinary Examination. The patient passed small amounts of amber-colored urine, which became dusky brown on standing exposed to the air. Quantity 300 to 500 c.c. per twenty-four hours. Routine examination: Specific gravity, 1010. Albumin, acetone, diacetic acid, bile, blood and indican negative. Microscopically, crystalline and amorphous urates, occasionally hyaline casts. The fresh urine containing the chromogen was amber-colored. It gave a dark brown coloration on being boiled with Benedict's solution, a slight amount of green precipitate settling out on standing. Reduced ammoniacal silver solution and alkaline picric acid solution. Unaffected by bromine water immediately, but on standing

[1] A preliminary report of this work was presented with Dr. B. S. Oppenheimer before the section of Internal Medicine, New York Academy of Medicine, March, 1916. In connection with the present study, further investigations of ochronosis were made by my former co-workers, Drs. B. S. Oppenheimer and B. S. Kline. On account of their absence on military duty the report of their work will be deferred until a later date.

a reddish coloration developed. With ferric chloride a green color was produced which vanished immediately. With lead acetate there was the usual white precipitate. With barium hydroxide a brown precipitate (melanin), the supernatant fluid becoming colorless. Boiled with strong nitric acid a yellow color is produced. Treated with potassium bichromate and sulphuric acid or with sodium hydroxide and potassium permanganate a dark brown to black color, evidently due to melanin, appears even in the cold. Black pigment formation readily took place on passing an air current through the urine made alkaline with sodium carbonate or sodium hydroxide.

All the subsequent tests and examinations were made on the urine after pigment formation had taken place. The urine, dusky yellow to black in color, reduced Benedict's solution immediately with heavy precipitate. Reduces picric acid solution, ammoniacal silver solution but not bismuth oxynitrate. Barium precipitates the bulk of the pigment. Lead acetate precipitates practically all the pigment, together with the urochromes, leaving a clear supernatant liquid. The urine does not form gas on fermenting with yeast. No rotation on polariscopic examination.

The presence of glucose could be excluded by the negative result of the fermentation test, optical inactivity of the urine and failure to reduce bismuth oxynitrate solution.

Attempts to Isolate Homogentisic Acid. In view of the tendency of homogentisic acid to decompose, the urine for this examination was collected in bottles containing a little dilute hydrochloric acid and preserved in an ice-box.

1. *According to Ester Method of Schumm.*[2] The total urine voided during three days, including portions containing the amber-colored chromogen as well as the melanin, was acidulated, and evaporated on the water-bath down to a volume of 300 c.c. which was extracted in Lind's rotary extraction apparatus for a period of five hours with ether. On evaporation of the ether about 3 c.c. of syrupy residue was obtained. The ether-soluble acids were evidently not increased in amount. The ethereal residue was dissolved in 200 c.c. alcohol, boiled one hour under a reflux condenser after the addition of 40 c.c. strong hydrochloric acid. The cooled liquid was diluted to about 600 c.c. with water, made weakly alkaline with sodium hydroxide and repeatedly extracted with ether. On evaporation of the combined ethereal extracts only a minute quantity of brown amorphous pigment matter remained. Neither homogentisic nor other esters, nor, indeed, crystalline substances of any kind, was found.

2. *According to the writer's procedure,* 3 liters of mixed urine were acidulated and evaporated to small bulk and extracted five hours

[2] München. med. Wchnschr., 1904, 1599.

in the special apparatus as previously. The small syrupy residue obtained on evaporating the ethereal extract was diluted with 100 parts of water and lead acetate added in excess. Aside from a small yellowish precipitate of resinous texture, which formed immediately, no other deposit appeared even on standing. The yellow precipitate was filtered off, dried, suspended in ether and decomposed by hydrogen sulphide. After removal of excess of hydrogen sulphide by an air current and the lead sulphide by filtration the residue left on evaporation of the ether weighed 0.1 gm. It crystallized out of water in small crystals which failed to lose water, also to sublime, and which melted at a temperature other than does homogentisic acid. *Homogentisic acid was therefore not present in the urine of this case.*

Method Employed for Preparation of the Melanin from Urine. This procedure depends on the writer's observation that maximum quantities of the pigment are precipitated from the melanotic urine by the addition of a like volume of 25 per cent. acetic acid to the neutral urine. Four hundred cubic centimeters of urine containing the chromogen was made distinctly alkaline by adding a little sodium carbonate solution and an air current passed through it for twenty-four hours. The pigment was fully developed from the chromogen at the end of this time. To the black urine an equal volume of 25 per cent. acetic acid was added and the mixture allowed to stand overnight. Owing to difficult filtration the supernatant fluid was removed from the precipitated pigment by means of a siphon and the pigment thoroughly washed by decantation with 12.5 per cent. acetic acid, employing twenty or more changes of the wash fluid. The melanin was next dissolved in a small amount of concentrated sodium carbonate solution and strong acetic acid added to neutralization. The pigment was then reprecipitated by the addition of a like volume of 25 per cent. acetic acid, collected on a filter, washed thoroughly with 12.5 per cent. acetic acid, twice with water, then dried in a desiccator, thoroughly extracted with alcohol, followed by ether and dried in vacuum. From 400 c.c. urine 0.55 gm. purified pigment could thus be obtained. The supernatant liquid obtained from the precipitation of pigment from the urine was evaporated to small bulk at a low temperature and the like volume of 25 per cent. acetic acid added. Additional melanin, 0.1 gm., was obtained in this way.

Additional pigment was obtained by boiling a costal cartilage with strong hydrochloric acid until solution took place, neutralizing, precipitating with an equal volume of 25 per cent. acetic acid and reprecipitating from 10 per cent. sodium carbonate solution, as in the case of the urinary pigment. 5.27 gm. air-dried rib yielded 0.120 gm. purified pigment. The rib pigment had the same characteristics as the urinary pigment.

The axillæ of the ochronosis patient were stained bluish black

with pigment particles which showed the same color reactions of the urinary pigment.

The pigment of the present case exhibited in general similar characteristics to melanins previously obtained from the urine and tumors of cases of melanosarcoma. Such pigments have been exhaustively studied by Mörner.[3] Accordingly the reactions found by this investigator to be characteristic for these tumor pigments were carried out on our preparations. The results of this comparative study are now mentioned. Barium hydroxide precipitated most of the pigment out of the urine. The precipitated melanin dissolved in various alkalies, sodium hydroxide, sodium carbonate, ammonium hydroxide, giving a black solution. From the sodium hydroxide solution the pigment could be precipitated by acetic acid added in excess. To the filtrate from the barium hydroxide precipitate, lead acetic was added. All the pigment, remaining in solution was precipitated. The pigment, filtered off, dissolved in sodium carbonate solution, but the addition of an excess of hydrochloric acid and saturation with magnesium sulphate failed to yield a precipitate (difference from Mörner's observation). The pigment, however, could be obtained from this solution on the addition of a like volume of 25 per cent. acetic acid.

The pigment was insoluble in water, alcohol and ether. Certain of Mörner's preparations showed a different solubility in acetic acid than is noted below. In judging of such results it must be emphasized that no method has as yet been discovered for isolating the melanin pigments with the help of indifferent chemical agents. It is therefore very probable that uncontrollable changes in structure may occur in the modes of preparation employed which can account for the failure of the observations of various investigators to be in strict accord. Thus it could be ascertained in our case that merely heating the pigment on the water-bath rendered it less soluble in alkali. In general it can, however, be stated that our preparations showed close similarity in their chemical behavior to the urinary and tumor melanin preparations obtained by Mörner.

Analyses of Urinary Pigment. A trace of iron and sulphur was found in the ash.

Ash determination, 0.5006 gm. of water-free pigment yielded 0.0439 gm. incombustible residue. Ash = 8.76 per cent. Determination of nitrogen by Kjeldahl. Preparation I, N = 10.81 per cent. Preparation II, N = 13.15 per cent. Determination of sulphur according to Carius. 0.1599 gm. water-free pigment gave 0.00865 gm. $BaSO_4$. S = 5.41 per cent. These analyses not calculated ash-free.

[3] For comprehensive literature concerning the melanin pigments see: Mörner, K. A. H.: Ztschr. physiol. Chem., 1886–87, xi, 66. Furth, O. v.: Centralbl. f. Allgem. Path. u. path. Anat., 1904, xv, 617. Oppenheimer: Handbuch d. biochem. Menschen u. d. Tiere, 1908, i, 743. Poulsen, V.: Ziegler's Beitr. z. path. Anat., 1910, xlviii, 346.

In regard to the value of the analyses it is again to be emphasized that the characteristics of this class of substances are so unfavorable that no claim of absolute chemical purity can be made for our preparations. This is evident from the results of the nitrogen and ash analyses which show considerable variation. Such discrepancies are, however, only to be expected in working with substances of this nature. The preparations are, however, probably as pure as others previously described, judging from the modes of preparation stated. The results of our analyses of the urinary costal and prostatic melanin preparations are compared in the following table with Mörner's analytical data. All of Mörner's analyses are included for reasons stated above. This comparison, if showing some variations, is seen to justify the conclusion that the pigments obtained by both workers are, if not identical, at least fairly closely related in composition.

COMPARISON OF ANALYSES OF MELANIN PIGMENTS.*

	Carbon.	Hydrogen.	Nitrogen.	Sulphur.	Iron.	Ash.
Mörner's preparations . .	55.7 to 58.1	5.9 to 8.0	11.08 to 12.30	4.75 to 10.18	Trace to (0.03 to 0.2)	2.02 to 9.38
Writer's preparations . .	55.7†	5.7†	11.84‡ to 14.41‡	5.93‡	Trace‡	7.45† to 8.76‡

* Elemental analyses calculated ash-free.
† Preparation from prostatic calculus.
‡ Preparation from urine.

Discussion of Results. The frequency of the association of ochronosis with alcaptonuria, the presence of joint lesions and characteristics of the urine (darkening on standing, reduction in the absence of glucose of alkaline copper and ammoniacal silver solutions) strongly suggested alcaptonuria as a probable diagnosis in this case. However, carefully executed systematic attempts to isolate homogentisic acid from the urine were uniformly negative. The excretion of a urine which darkens on standing is not specific for alcaptonuria for such cases of melanuria without alcaptonuria have been previously reported. The melanuria of carbolic acid poisoning can also be excluded in the subject of the present studies. In the urine, prostate and ribs, therefore, very probably generally distributed in the body, could be isolated a pigment, found by analyses and chemical characteristics to be related to the protein melanins. The presence of sulphur and iron in this pigment excludes definitely any direct origin from homogentisic acid which contains neither of these elements. On the grounds thus enumerated the diagnosis of alcaptonuria can be excluded.

The reduction of alkaline copper and ammoniacal silver solution is common to various aldehyde substances and is therefore by no means characteristic of homogentisic acid. As alkaline solutions

of the isolated and purified pigment failed to give these reactions they are probably to be ascribed to a chromogen of aldehyde nature. *Owing to these findings and considerations the writer does not consider it in general advisable to accept a positive diagnosis of alcaptonuria in a given case without the isolation of pure homogentisic acid and its proper chemical identification.*

The urinary pigment had the same characteristics as that obtained from the costal cartilages. The pigment in other parts of the organism, so far as its quantity enabled examination, showed no obvious differences from that obtained in the urine and rib cartilages. Evidently but a single melanin was present. This pigment was compared as to its reactions with those described by Mörner for melanin obtained from the urine and tumor of a patient suffering with melanosarcoma. In most characteristics these melanins showed agreement. The analyses made in both cases were also in reasonable accord. These grounds seem sufficient to establish a relationship between the pigment obtained from this case and the tumor melanins which are closely related to protein. It may also be mentioned that such melanins very probably consist of large and complicated molecules for such complex substances as methyldibutylacetic acid,[4] xyliton,[5] and pyridin[6] have been obtained from them. It would be very difficult to imagine the formation of such complicated bodies from pigment derived from carbolic acid and homogentisic acid which are simple phenol derivatives. This may be regarded as an additional reason for accepting that the *pigment under discussion is to be regarded as of complex nature allied to the protein bodies.*

Pathogenesis of Ochronosis. Including the present case reports from 40 individuals exhibiting the symptom-complex of ochronosis have been published. Three groups of these cases can be readily separated according to their etiology as follows:

1. Ochronosis due to carbolic acid poisoning.
2. Ochronosis due to alcaptonuria.
3. Ochronosis due to other causes than (1) and (2).

In the first group, 9 in number, the coloration has very gradually developed after copious and continued applications of carbolic acid to chronic surgical lesions. The origin of the color is evidently from the poison mentioned, for a certain degree of recovery has been reported to ensue on cessation of the phenol treatment.

Into the second group, ochronosis associated with alcaptonuria, fall somewhat more than half of all cases hitherto described. In our review of these reports it was noted that frequently the diagnosis of alcaptonuria had been based practically solely upon the observation of urine which darkened on standing and exhibited reducing

[4] Speigler, E.: Beitr. z. chem. Physiol. u. Path., 1903, iv, 40.
[5] Wolf, H.: Beitr. z. chem. Physiol., 1907, v, 476.
[6] Furth, O. v., and Jerasulem, E.: Beitr. z. chem. Physiol. u. Path., 1907, x, 131.

properties. The extensive study made in the present case has demonstrated the unreliability of such a diagnosis when it fails of corroboration through the presence in the urine and satisfactory identification of the alcapton body, homogentisic acid. In view of this it seems probable that certain cases hitherto confidently described as alcaptonurics may in reality represent ochronosis without alcaptonuria. The actual number of cases exhibiting ochronosis in company with alcaptonuria where homogentisic acid has been unquestionably identified is but a small fraction of those included under this diagnosis in the literature.

In the third group of cases belong the cases studied by v. Hanseman,[7] Salkowski[8] and Langstein.[9] Alcaptonuria and medicamentation, which could lead to melanuria, were excluded, although certain criticisms can be offered to this work. The same holds true for Hecker and Wolf's[10] patient. As stated a number of apparent alcaptonuric cases are possibly to be included in this category. The present case represents the first of these doubtful cases to be subjected to a thorough chemical study, including isolation of the pigment in a purified state and its analysis. The resulting diagnosis, that of ochronosis unaccompanied by alcaptonuria, though representing nearly a unicum in the literature, may, however, be fairly regarded as placed on a firm basis as a result of this detailed investigation.

On first sight any attempt to reconcile these wide clinical variations to a common cause seems quite hopeless. Why should an extraneously applied poison, as is phenol lead to the identical clinical symptoms as appear in connection with a definite disorder of intermediary metabolism (alcaptonuria) and at the same time be found in other cases quite distinct from either of these conditions? The first insight into the real nature of ochronosis was, however, afforded by Pick,[11] who put forward the view that through the action of the oxidative ferment tyrosinase, phenol substances were changed into melanin pigment. Abderhalden and Guggenheim[12] have in recent years materially added to our knowledge of the formation of melanin by the action of this ferment. They found in extended and comprehensive studies that simple phenol compounds, homogentisic acid, the amino acid tyrosin and polypeptids containing tyrosin were all acted upon by tyrosinase, with the resulting formation of melanin pigment. All these substances contain the oxyphenyl group and can be designated by the general formula $R.C_6H_4.OH$, in which

[7] Berl. klin. Wchnschr., 1892, xxix, No. 27, 660.
[8] Ibid., p. 661.
[9] Beitr. z. chem. Physiol. u. Path., 1904, iv, 145; Berl. klin. Wchnschr., 1906, xliii, 597.
[10] Festschr. z. Feier d. fünfzig jahrigen Bestehens d. Städt. Krankenhaus zu Dresden-Freiderichstadt, Dresden, 1899, 323.
[11] Pick, L.: Berl. klin. Wchnschr., 1906, xliii, 591.
[12] Ztschr. physiol. Chem., 1907–08, liv, 331.

R may represent hydrogen or a complicated group. A peculiar specificity in the action of this ferment could also be demonstrated, inasmuch as it did not effect phenylalanine, the amino acid closely related to tyrosine, nor indeed diiodotyrosin. In phenylalanin and diiodotyrosin the hydroxy group (—OH) is absent although the benzine ring is represented in both these substances. The conclusion may therefore be drawn that for the development of pigment by the action of tyrosin the oxyphenyl group $R.C_6H_4.OH$ is necessarily present.

Application of these important studies to the pathogenesis of ochronosis has, however, not yet been made, although they represent the key to a clearer comprehension of the etiology of this condition. From Abderhalden and Guggenheim's studies it may be reasonably presumed that an accumulation of excessive and abnormal amounts of substances within the organism possessing the oxyphenyl group would lead to the production of melanin pigments by ferment action. This seems to be borne out by the clinical observations on carbolic acid poisoning and alcaptonuria, both these substances containing this chemical entity.

In seeking a possible explanation for those obscure cases, including the present one, where both of the above evident causes of the ochronosis fail to be present, the observation of pigment formation from higher compounds such as polypeptids, closely related to protein, becomes of interest. It seems not unlikely from the number and complexity of the split products of such melanins which have been observed that this class of the black pigments may indeed be of very complex constitution. Their tyrosin content may, however, be responsible for the development of the pigmentation owing to the oxyphenyl group contained in this amino acid. The tumor and other protein melanins among which the example here described apparently belongs probably owe their origin to a metabolic anomaly of this nature.

Just how important a part is played by ferments in this pigment formation is, owing to the absence of definite evidence, still a matter of speculation. Still the ferment tyrosinase is now known to be extensively distributed in animals, having been found in the skin and even in melanosarcomata It is then probable that tyrosinase is normally present in the organism. It seems then fair to assume that the action of this ferment on chromogenic substances such as tyrosin, tyrosin-containing complexes, homogentisic acid, phenol, etc., when present in increased amounts within the body is the ultimate cause of the ochronosis symptom-complex.

Although sulphur and a trace of iron were present in the pigment of this case, this seems no ground for regarding this melanin to be of blood origin. According to von Fürth,[13] who has extensively

[13] Fürth, O. v.: Oppenheimer's Handbuch. d. Biochem. Menschen. u. d. Tiere, Jena, 1908, i, 743.

studied the melanins, iron and sulphur groups are to be regarded not as primary in such pigments for which the oxyphenyl group is characteristic. Indeed sulphur is frequently entirely absent or present in an amount much greater than it is represented in hemoglobin which facts preclude of accepting the blood pigments as the mother substances of the melanins.

The Relation of Ochronosis to Alcaptonuria. Ochronosis frequently accompanies alcaptonuria and it may be reasonably assumed from the foregoing considerations that the pigmentation of alcaptonuria is due to a melanin arising from homogentisic acid. This view is accepted by Gross and Allard[14] as follows:

"Die Ochronose und die Alkaptonurie sind Erscheinungen ein und derselben Stoffwechselerkrankung, die klinisch in der Ausscheidung von Homogentisinsäure, der Alkaptonurie und oft in arthritischen Beschwerden, pathologisch-anatomisch in der Ablagerung eines Farbstoffs, der Ochronose, ihren Ausdruck findet."

Although it is probably true that the ochronosis and alcaptonuria when occurring simultaneously are indeed to be regarded as "expressions of the same metabolic disease," all cases of ochronosis certainly cannot be properly ascribed to alcapton origin as is the evident opinion of these authors. The nine known cases of ochronosis due to carbolic acid intoxication as well as the others, including the present one, enumerated above where alcaptonuria could be excluded, militate against the acceptance of this theory. It may also be mentioned that in alcaptonurics the signs of ochronosis have been found absent also on postmortem section.[15] The views concerning the pathogenesis of these conditions described in the preceding pages of this article seem sufficiently comprehensive to establish the general relationship of these rare anomalies of metabolism.

RELATION OF THE PHYSICAL SIGNS TO THE ROENTGEN PLATE IN PULMONARY TUBERCULOSIS.[1]

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There has been considerable controversy as to the value of the roentgen-ray findings in reference to the diagnostic benefit in pulmonary tuberculosis. In order to obtain the greatest benefit

[14] Mitt. aus d. Grenzgeb. d. Med. u. Chir., 1908–09, xix, 24.

[15] Fürbringer, P.: Berl. klin. Wchnschr., 1875, xii, 330. Moraczewski, W. v.: Centralbl. f. inn. Med., 1896, xvii, 177.

[1] Read before the St. Louis Medical Society.

from a plate it is absolutely necessary to compare the physical signs with the shadows seen on the plate.

In a broad sense the same factors which alter sound vibrations alter light vibrations. Sound and light are therefore, more or less, of the same character. Light waves, however, travel many times more rapidly than sound waves, consequently the physical signs which constitute variations of sound waves may be correlated with the roentgen plate which gives the variations of light waves. It is the purpose of this paper to discuss the relation of physical signs to the finished plate.

There are a large number of charting schemes, especially one by Sahli, that are in use in various parts of the country, by which anyone familiar with the chart can easily interpret the findings. The method that I use in our clinic is one that I found much simpler than the one in vogue, and one is enabled to interpret the findings in terms of physics:

The scheme is as follows:

MS—muscle spasm.
B S—breath sounds.
WS—whisper sounds.
VS—voice sounds.
VF—vocal fremitus.
T F—tactile fremitus.
+ + + + —plus represents the degree of increased intensity.
– – – – —minus represents the degree of decreased intensity.
/ / / / / / / —parallel lines in one direction represent impaired resonance.
—parallel lines in two directions represent dulness.
▩▩▩▩ —parallel lines in three directions represent flatness.
× × × × —denotes rales, the character of which is written in the margin.

While this scheme of charting is not perfect it helps to interpret the relation of physical signs in terms of physics.

BS—breath sounds—represent the number of vibrations set up in the chest wall as heard through a stethoscope, and are due to the vibrations set up by the passage of air into the bronchus through the bronchioles and vesicles, altered more or less by the character of the medium through which the sound waves travel.

WS—whisper sounds—represent the waves set up in the chest wall by the whisper, altered, more or less, by the medium through which they travel.

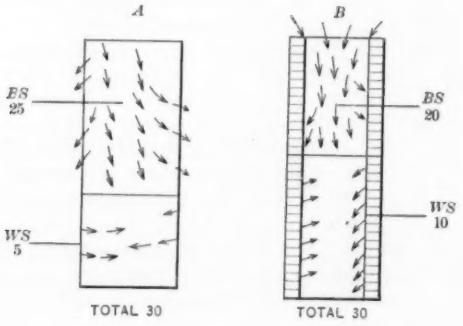
For the sake of convenience I use the symbols *BS* two plus and *WS* one plus and no impairment of resonance as the normal type of breathing (normal vesicular breathing).

In order to demonstrate the theme of the paper I will present the following hypothesis:

Let *A* represent a bronchus or bronchiole, with thin walls over

which one hears thirty vibrations per second on the chest wall, due to the act of taking a deep breath. Let *B* represent a bronchus or bronchiole, with dense or infiltrated walls over which one hears approximately the same number of vibrations. In order to explain the phenomena we must know that sound waves travel indefinitely, although we have no means as yet by which to recognize them as sound beyond a certain distance from their source. The transmission of these waves depends on the density of the substances through which they travel—some substances retard the vibrations while others increase the vibrations by being set in resonance in unison, in this way increasing the number of sound waves.

The Physics of Chart A. Thirty-five vibrations per second are set up by the passage of air into the bronchus—the walls being thin, some of the vibrations will pass on through the wall, leaving twenty-five to be heard over the area while five have been added by the resonance of the thin walls.



The Physics of Chart B. From the same deep breath as taken in Chart A only twenty vibrations could enter the bronchus on account of the thickened walls and none of these twenty could penetrate the dense walls, consequently they were confined—the force, however, has set the walls in resonance, which adds ten vibrations. Thus we have the same number of vibrations over both bronchi but produced by different causes.

A roentgen-ray picture of *A* would show the lines thin and far apart while the picture of *B* would show dense lines with only small air content.

The physical signs of *A* and *B* give one the same mental picture as the roentgen-ray shadows—the one viewed by variation of sound waves while the other by variation in light waves.

It is necessary here to admit that the roentgen ray permits one to recognize differences in light much more easily than the ear

perceives differences in sound; but when one uses the ear and the eye together, with logical deductions, one cannot go very far astray in proper conclusions.

The skiagram is only part of the physical signs of the chest, and to interpret them as having any effect on the patient's condition one must look to symptoms, temperature record, history and other findings.

I will attempt to demonstrate the value of correlating the physical signs with the roentgen plate by describing first the roentgen plate and then the physical signs as elicited by careful examination.

CHART I.—Case 1.

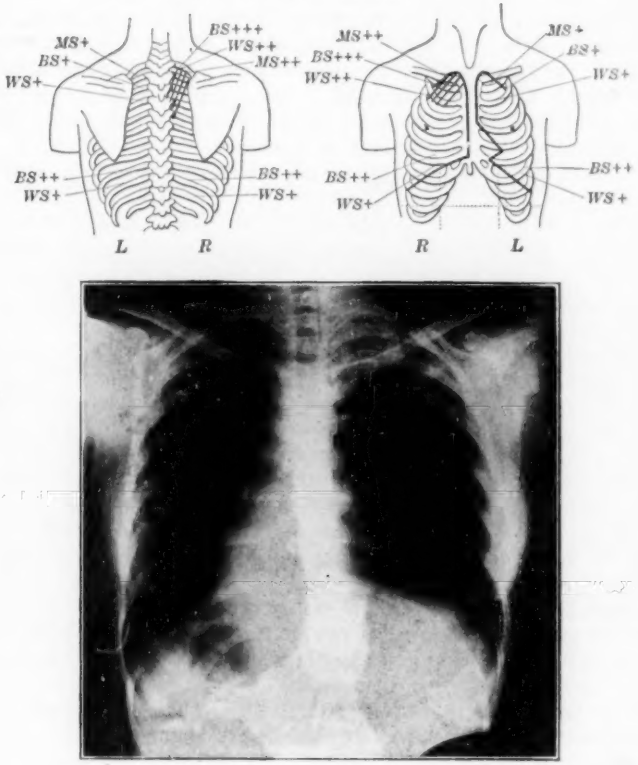


CHART I.—The plate being a flat picture all parts of the chest are in one plane, consequently it is impossible from the picture to interpret whether the shadows seen are anterior or posterior, but the physical signs show where one can put the shadows in their proper relation even without a stereoscopic picture.

The right upper: One sees a thickening of the interlobular lines and moderate approximation and interlacing. Here and there air-containing spaces are noted. The lines in the lower lobe are distinct, not thickened, and there is considerable air-containing spaces. The diaphragm on the right side is rounded and the costal angle is deep. In the left chest, upper portion, there is a moderate thickening of the interlobular lines, with no approximation. The air content is good. In the lower lobe the lines are not thickened. The diaphragm is rounded and the costal angle is deep.

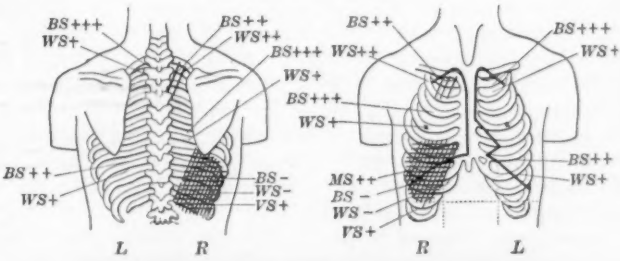
PHYSICAL SIGNS. Anterior on the right we have impaired resonance and two-plus muscle spasm. The breath sounds are harsh and whispered sound is increased. In the lower lobe the breath sounds are normal as well as the whisper, with no impairment of resonance. The left chest, upper part, muscle spasm, one plus. The breath sounds are relatively diminished and the whisper is normal, with no impairment of resonance. In the lower part, anterior, the breath sounds are normal, two plus, whispered sound one plus, with no impairment of resonance.

Posterior, right upper, muscle spasm is two plus, breath sounds three plus, whispered sound two plus and resonance is impaired. Lower part is normal—breath sounds two plus and whisper sound one plus. Posterior, left upper, muscle spasm one plus, breath sounds one plus, whispered sound one plus, with no impairment of resonance noticeable. Lower left is normal: breath sounds two plus, whispered sound one plus.

Correlating the physical signs with the shadows seen on the roentgen plate we must come to the same conclusion in the light of the physics of sound and light. The physical signs in the right upper, anterior and posterior, shows a three-plus breath sound and a two-plus whisper, with an impairment of resonance, a syndrome, as it were, which could only be produced by a moderate infiltration of the tissues in which were air-containing spaces. The increase in whisper demonstrates that the walls of the tubes are thickened and have added more vibrations to the breath sounds as explained in Fig. B. If the walls are thickened we can readily understand the impairment of resonance as found by percussion. In the plate the interlobular lines are thickened and approximated, a condition producing a shadow in which the air content is small and proves that only a small amount of air-borne vibrations are taken in the lung. The muscle spasm over the right upper, anterior and posterior, is more marked on the right than on the left, which condition is interpreted as activity. In the left upper part of the chest plate we see a moderate thickening of the interlobular lines, but with considerable air space, a condition noted by physical signs by the diminished breathing, with no impairment of resonance. The lower part of both lungs in the plate shows the lines far apart and not thickened, with considerable air space. A like interpretation was given to the physical signs, denoted by breath sounds two

plus, whisper one plus. We see here an agreement of physical signs and roentgen-ray plate, but the plate gives a more graphic picture of actual lung condition, and one feels much surer of his findings when the variation of sound waves demonstrated by physical examination is verified by the roentgen plate.

CHART II.—Case 2.



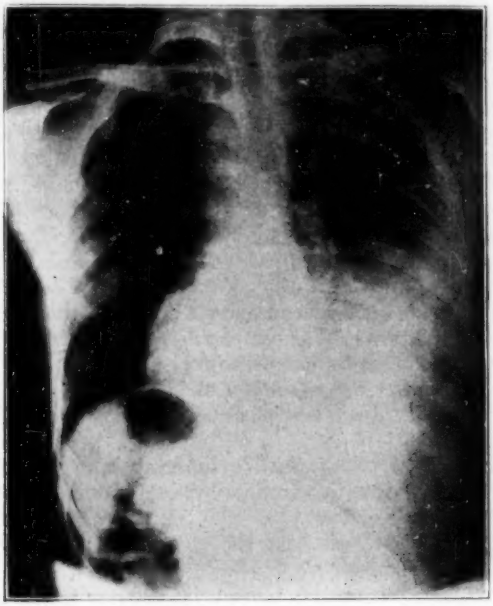


CHART II.—Air content good in the left lung. The hilus is fairly dense, with a few small nodules. Interlobular lines visible, but not approximated or thickened. The costal angle is deep. On the right, upper portion, the interlobular lines somewhat thickened and very closely approximated, especially in the upper portion, while

below this the lines are indistinct and there is considerable air space. The hilus is compressed. A homogeneous shadow extends from the seventh posterior rib and shades into the shadow of the liver. Shadow of the diaphragm not visible. No costal angle seen.

PHYSICAL SIGNS. CASE 2. Anterior on the left we have loud breath sounds three plus, whisper one plus, and hyperresonance. The lower portion, breath sounds and whisper normal. On the right, anterior, there is an impairment of resonance in the upper part, with normal breath sounds, but the whisper is increased, two plus. From the second to the fifth rib we have an area of increased breath sounds three plus, with whisper one plus, compensatory emphysema. From the fifth rib to the last rib there is an area of flatness, with muscle spasm marked, two plus, breath sounds and whisper sounds not heard and the voice sound barely transmitted.

Posterior on the left similar to anterior, while on the right the flatness begins at the seventh rib.

Correlation of Physical Signs and Roentgen Plate. The physical signs show an impairment of resonance in the right upper, anterior and posterior, with increased whispered sounds and no noticeable increase in breath sounds, a condition which indicates an area of lung in which there is less air than normal, the two-plus whisper indicating a congestion or compression of the lung tissue. In the plate we find the interlobular lines closely approximated, not thickened, a condition which definitely shows that less air was in that part of the lung. The hyperresonant area indicated on the chart is demonstrated on the plate by the "brilliant" condition, which shows that a great deal of air was in that part of the lung.

The flatness seen in the lower part of the lung shows by the diminished breath and whispered sounds that no air was in that part of the lung (lost by diffusion of vibrations). The shadow seen on the plate, being homogeneous, shows a like condition, that is, no lung tissue in that area. The compression of the hilus demonstrates that the entire lung is compressed from below.

We again see here an agreement of the physics of light and sound. The condition was diagnosed pleural effusion and was proved by thoracentesis.

CONCLUSIONS. 1. It is possible in most cases to predict the roentgen findings after a careful physical examination has been made.

2. One can show by charting the physical signs as indicated in the paper in terms of physics.

3. Every available means should be used to assist us before interpreting conditions hidden from our sight before hazarding a definite diagnosis.

4. The shadows seen on the roentgen plate is only a physical sign.

NOTE.—Unfortunately a print of a roentgen plate does not bring out the finer lines, consequently the demonstration of the prints is not as conclusive as one would like.

A CASE OF CONGENITAL ABSENCE OF THE UTERUS WITH ANOMALOUS VULVOVAGINAL ANUS.

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In May, 1915, a Chinese girl, aged twenty years, entered the Wilhelmina Hospital, Amoy, China, with the complaint that her menstrual flow came from the urethra instead of from the vagina. The patient was extremely timid, and her mother had to state her case.

Upon external examination it was found that the pubic hairs were scant, but this is usual among the Chinese. There was a complete absence of anal opening at the usual site. Clitoris, labia and urethra were normal. The vaginal opening was rather small, and there was no trace of a hymen.

Upon internal examination no uterus could be felt, but one could feel a broad band in the pelvis stretching from side to side, and sagging somewhat in the middle. On the right side near the pelvic brim there was in this band a small gland-like object, about 2 cm. in diameter. No gland was palpable on the left side. On examining the posterior part of the cavity it was found to be very roomy. There was no septum dividing the vagina from the rectum. The examining finger came in direct contact with feces in the rectum. By introducing a sound into the bladder and two fingers into the rectovaginal cavity no uterus could be felt. The bladder seemed to be without defect. By the aid of a speculum our previous findings were confirmed and no further trace of a uterus could be found.

The patient's breasts were normally developed and she had a normal feminine voice and appearance. She was kept under observation in the hospital for about two months to determine whether we were probably dealing with a case of vicarious menstruation. But during that time no signs of menses appeared.

These findings were confirmed by J. Henderson Lamb M.B. (Edin.), of Chang-poo, China, and Miss W. Murman, accoucheuse (Amsterdam), and head nurse in the Wilhelmina Hospital, Amoy, China.

Absence of the uterus is considered sufficiently rare to merit report. That it is not as rare as earlier writers have believed is shown by the increase of the number of cases reported in recent literature. From time to time there have been attempts to collect and classify the cases that have been described. Among the earlier attempts were those of Thudicum,[1] Fürst[2] and Kussmaul.[3] In

[1] Monatsch. f. Geburtsh. und Frauenkr., Berlin, 1855, v, 272–289.
[2] Ibid., 1867, xxx, 119; 161.
[3] Von dem Mangel, der Verkümmerung und Verdopplung der Gebärmutter, 1859, Würzburg.

1897 Burrage[4] reviewed the literature and collected 360 cases reported by 239 different writers.

Since the review by Burrage, 76 cases have been reported by 66 different writers. This includes those of 1896, since they were probably not included in the previous review. In only 51 cases was the literature accessible. The only data obtainable in the others were from what appears in the titles of the articles.

Of the 51 cases in which the literature was accessible, 1 was diagnosed at autopsy, 1 was found during dissection and 7 were confirmed by abdominal operation. The others were diagnosed in the living subject. Such a diagnosis is not always reliable, since bands of muscle may be present which morphologically represent the uterus but which cannot be detected by ordinary methods of examination. But for practical purposes we may accept such diagnoses.

Burrage finds that the absence of ovaries in conjunction with absence of the uterus is exceedingly rare. Previous to 1897 there were only 6 cases on record, and in only 3 was the diagnosis verified postmortem. Since then 26 such cases have been reported. The case of Sloan[5] was discovered at autopsy and the case of Forbes[6] during dissection. In the case of Lynds[7] an operation was performed and no ovaries were found, but by microscopic examination of the tumor which was removed, Warthin discovered a rudimentary ovary.

The absence of tubes in cases of congenital absence of the uterus is equally rare. Burrage reported 6 cases, of which only 1 was confirmed at autopsy. We found 18 cases reported in recent literature, 4 of which we must accept without question, viz., those of Sloan, Forbes, Lynds and Van Bockstaele.[8] Borelius[9] and Smith[10] each reported a case in which there was absence of only one tube and one ovary. Both of these cases were confirmed by operation.

Among the 76 cases there were only 3 in which the ovaries (or in one case perhaps the testes) were found in the inguinal canal. These were the cases of Gillmore,[11] Swasey[12] and Cullen.[13] Engleish[14] previously reported 38 cases of ovarian hernia, of which 27 were inguinal.

It has been said that in the majority of cases of absence of the uterus there is also absence of the vagina or a rudimentary develop-

[4] Am. Jour. Med. Sc., 1897, n. s., cxiii, 310–321.
[5] Phil. Med. Council, 1896, i, 140.
[6] Montreal Med. Jour., 1901, xxx, 848.
[7] Jour. Mich. Med. Soc., Detroit, 1905, iv, 122.
[8] Jour. Méd. de Brux., 1913, xviii, Supplement 91.
[9] Hygiea, Stockholm, 1896, lviii, pt. 2, 190–192.
[10] Ann. Gyn. and Pediat., Boston, 1905, xviii, 169–172.
[11] Am. Jour. Obst., New York, 1906, liii, 520–525.
[12] Am. Med., Philadelphia and New York, 1907, n. s., ii, 519–521.
[13] Surg., Gyn. and Obst., Chicago, 1910, xi, 73–75.
[14] Jahrbuch. der K–K. Gesellschaft der Aerzte in Wien. 1871.

ment of the same. We have found that there were 29 cases of absence of the vagina and 20 cases of rudimentary development. This forms more than 60 per cent. of the total number.

In all the literature on this subject we have been able to find only 3 cases in adults in which an anomalous vulvovaginal anus was associated with congenital absence of the uterus, viz., those of McCann,[15] Bullard[16] and Lurier.[17] Bosquet,[18] in 1757, mentions the case of an infant, which died at birth, in which there was a persistent cloaca, absence of the uterus and absence of the bladder. There may have been other cases in monstrosities, but the above mentioned are the only ones reported in adults.

In McCann's case there was a rudimentary uterus present, but the rectovaginal septum was incomplete. Bullard's findings are briefly as follows: The external genitalia were normal; there was no evidence of a uterus; there was a fibrous band extending from one side of the pelvis to the other; the ovaries seemed to be present but small; there was no normal anus but the rectum communicated with the upper end of the vagina about 2.5 or 3 cm. from the ostium, and at this point there seemed to be an annular constriction resembling a sphincter ani. In Lurier's case there was an absence of the uterus and vagina and the anus was found in the usual position of the vagina, opening below the fossa navicularis. There was a horizontal band between the rectum and the bladder, which Lurier considers might probably be a rudimentary uterus.

Although absence of the uterus is considered rare the occurrence of an anomalous vulvovaginal anus is much more rare. Von Bardeleben[19] estimates that there is one such case in every 25,000 or 30,000 births. In the cases mentioned above and in the one just reported there has been a failure in the development of the septum which separates the urogenital sinus from the rectum as well as a failure in the development of the Müllerian ducts. It is not necessary to enter into a discussion of the development of the genitalia or of the rectovaginal septum, since this has been thoroughly covered in recent articles. We have merely given a general survey of the recent literature on the subject of absence of the uterus and have grouped the few cases which, like the one just reported, have an associated anomalous vulvovaginal anus.

[15] Am. Jour. Med. Sc., 1896, n. s., cxii, 393.
[16] Jour. Am. Med. Assn., 1898, xxxi, 479.
[17] Deutsch. med. Ztg., Berlin, 1904, xxv.
[18] Recueil periodique d'observations de Méd. Chir. et Phar. ou Jour. de Méd., vi, 128, 1757.
[19] Arch. f. Gynäk., Berlin, 1903, lxviii, 3–56.

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3. Bell, C. E.: Ibidem, 1904, ii, 1751.
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CLINICAL EXPERIENCE WITH KOGA'S CYANOCUPROL.

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The problem of tuberculosis therapy is one of the most absorbing and elusive in medicine. Koch's epoch-making invention of tuberculin was accepted at first with the greatest interest not only by the medical profession, but by those who were suffering from the disease. Its therapeutic value, however, was not as great as anticipated, while, on the other hand, so many disadvantages were detected in the form of so-called reactions that it finally came to be considered not only useless but actually injurious, and its clinical application was practically given up. Subsequently many improvements were attempted by Koch himself and many others until more than forty preparations have been reported, none of which seems to be either efficacious or entirely free from harmful reactions.

Since Ehrlich and Hata obtained such brilliant success in the treatment of syphilis with salvarsan many attempts have been made to discover a remedy for the treatment of tuberculosis on similar principles. In April of last year, at the annual meeting of Kenkyusho Dosokwae (Association of the Fellowship of Kitasato Institute for Medical Research), Dr. Koga read a paper reporting the success in animal tests as well as in the clinical application of his own antituberculosis remedy. The new preparation, which has been named cyanocuprol, is the compound salt of potassium cyanide with copper (as may easily be inferred from the name), the exact chemical composition of which has not yet been reported. He began his experiments with potassium cyanide, and he found that in some animals its use resulted in a distinct healing tendency. In most cases, however, the destructive process was most evident because of the strong toxicity of the drug. He experimented further, trying to prepare some other compound which would be more effective and less poisonous. The new preparation which he succeeded at last in making was suggested by Koch's "aurum kalii cyanatum" and Linden's copper compound. After several series of animal tests, he concluded:

1. That guinea-pigs previously inoculated with tubercle bacilli and then treated with this preparation do not die of the infection or at least their lives are prolonged in comparison with the control animals.

2. That the drug has considerable healing ability, as shown by the condition of the affected organs at autopsy and by subsequent histological study. There is marked influence in the stimulation of formation of new tissue from surrounding parts, and the tubercle bacilli contained in them are in some instances entirely killed. Inoculations with pieces of such organs into healthy animals cause no tuberculous process.

3. That the injection of the drug, if begun at the time of inoculation or within four days from it, does not prevent the onset of tuberculosis. After the formation of nodular tubercles, however, it begins to manifest its influence upon them.

4. That some signs of reaction are constantly observed after the injection in the form of local hyperemia and infiltration of round cells, followed finally by proliferation of fibroid tissue (encapsulation).

5. That too large doses are distinctly harmful, because a softening of the tubercles and a generalization of the process is caused and the animal dies.

From the foregoing statements we may assume that the preparation is by no means germicidal, except in a secondary way. It shows little parasitropic nature, while the organotropic property seems to be great, and so it may not be called a strictly chemotherapeutic remedy, according to Ehrlich's definition. Yet a favorable influence is experimentally proved with certainty.

Koga proceeded further to apply this remedy to 125 patients. The results are shown in the following table:

	Number of patients.	Cured.[1]	Improved.[2]	Died.	Treatment discontinued.	In course of treatment.
Passive cases:						
1st stage . . .	19	13	2	0	1	3
2d stage . . .	6	3	3	0	0	0
3d stage . . .	4	1	3	0	0	0
Active cases:						
1st stage . . .	7	4	2	0	0	1
2d stage . . .	11	3	5	0	1	2
3d stage . . .	8	0	3	3	0	2
Surgical tuberculosis	8	1	4	0	2	1
Total	63	25	22	3	4	9

LOCAL REACTIONS. On the day after injection a slight dulness and rales appeared over the affected spot, where no such physical symptoms were evident before the injection, or if such signs were present, they increased in degree and extension. In from seven to nine days the reactions disappear.

In cases of skin tuberculosis the affected parts become reddened and swollen, painful to pressure, and sometimes suppurative. After ten days this reaction entirely disappears. In 5 cases of glandular tuberculosis the swollen glands became painful and the swelling increased. The pain and swelling gradually decreased after five days until the glands were somewhat smaller than before. On the next injection they again became painful and swollen, but less intensely than before, and after from five to seven injections they were completely absorbed. In 1 case the suppurating gland broke through to the surface of the skin, but healed without leaving behind a fistula. In 1 case of renal tuberculosis the kidney became swollen and painful, hematuria followed on the day after injection, and the general condition became worse, but in seven days all symptoms gradually decreased. The pain at the time of urination diminished and the turbid urine became clear and transparent.

All of these reactions were much less intense in patients who had been treated previously with tuberculin.

TUBERCLE BACILLI IN SPUTUM. Of 8 patients of the second and third stages the sputum was examined every day, with the following result: From the day after injection the number of bacilli was gradually increased, reaching the maximum point on the fourth or sixth day, when it began slowly to decrease. After from seven to ten days the number was obviously smaller than before the injection, and after repeated injections the bacilli disappeared

[1] Body temperature constantly below 37° C. Absence of clinical symptoms. Patients are able to go on with their work without trouble.

[2] Symptoms much reduced but not entirely absent.

entirely in favorable cases. Morphologically the bacillus undergoes striking change. In one to three days after the injection the coloring of some bacilli became fainter and homogenized, granular construction was lost, and some were cut into pieces and in appearance resembled streptococci or staphylococci.

FEVER. In some cases, at the first and second injections, the temperature rose to 38° to 40° C. after several hours, then fell gradually to normal in three to seven days. Among 10 highly feverish patients 3 became afebrile after the first injection, 3 after the second, and 3 after the third, while 1 case was entirely unaffected. In all other cases no influence was evident.

BODY WEIGHT. In most cases the body weight decreased (500 grams or more) immediately after the injection, only to be almost restored in a few days or in two weeks at the latest. In exceptional cases the body weight increased a little after the first injection.

SUBJECTIVE SYMPTOMS. Cough and expectoration are usually relieved after the injection and the patient feels fairly comfortable.

ACCESSORY ILL EFFECTS. No remarkable symptoms may be noticed as accessory ill effects of the remedy itself. Sometimes if the solution is injected too rapidly the patients complain of an uncomfortable feeling on the chest and of palpitation of the heart immediately after the injection. In most cases night-sweats are complained of for two or three days after the injection.

DOSES. As shown in the animal experiments too large doses are injurious. The doses suggested by Koga are as follows:

For incipient cases, 7 to 9 c.c.

For advanced cases, 6 to 7 c.c.

Doses should be given intravenously and repeated five to ten times at intervals of two weeks or more. This interval was proved most satisfactory by animal tests. It should never be shortened.

CONTRA-INDICATION. The treatment is contra-indicated for those in whom the respiratory surfaces are too much affected or the general condition too seriously weakened.

EFFECT OF OTHER DRUGS ADMINISTERED DURING TIME OF TREATMENT. Aq. lauroc., creosote, guaiacol, and iodin preparations should not be used during treatment with cyanocuprol.

Koga's paper was received with great interest. He was unwilling, however, to offer the remedy immediately for public use, but felt that it should be tested further on the sick bed, not only by himself but by many other skilled practitioners, in order that an impartial estimate might be made of its therapeutic value and that the details of its practical application might be thoroughly worked out. For the purpose of this investigation twenty well-known hospitals and sanatoria were asked, in the name of Prof. Kitasato, the president of the institute, to try this preparation on the sick bed. Accordingly, we began to use it in May, 1915, and up to the end of 1915 about two hundred patients had been treated. We

collect here a record of the experiments of this period and will report the general result. Of course this period of half a year is too short to make any definite statement, especially with regard to the therapeutic value of a preparation for a chronic disease like tuberculosis, the total course of which may extend over several years. What is said here, therefore, is necessarily of temporary validity. Whether this result may be of ultimate value can be decided only by further observations.

We may summarize the total results in the following table:

TOTAL NUMBER OF PATIENTS TREATED.

	At Tennoji.	At Hamadera.
1st stage	17	21
2d stage	36	57
3d stage	23	29
	76	107

TOTAL RESULTS OF THE TREATMENT.

AT TENNOJI.

	1st stage.		2d stage.		3d stage.		Total.	
	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.
Cured	10	58.8	9	25.0	0	0	19	25.0
Much improved	6	35.3	20	55.5	6	26.1	32	41.2
Somewhat improved	1	5.9	5	13.9	14	60.9	20	26.4
Remaining unchanged	0	0	0	0	2	8.7	2	2.6
Worse	0	0	1	2.8	1	4.3	2	2.6
Treatment discontinued	0	0	1	2.8	0	0	1	1.3
	17	..	36	..	23	..	76	

AT HAMADERA.

	1st stage.		2d stage.		3d stage.		Total.	
	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.	No. of patients.	Per cent.
Cured	16	76.4	9	15.8	0	0	25	23.4
Much improved	4	19.1	28	49.1	4	13.8	36	33.7
Somewhat improved	1	4.8	16	28.7	19	65.5	36	33.7
Remaining unchanged	0	0	1	3.5	3	10.3	4	3.7
Worse	0	0	0	0	2	6.9	2	1.8
Treatment discontinued	0	0	3	5.4	1	3.4	4	3.7
	21	..	57	..	29	..	107	

The stage is decided upon by a comparison with the standard given by the Bureau of Hygiene of Germany.

Cured: No fever, objective and subjective symptoms absent, and patients are able to go on with their work without feeling any inconvenience. No bacilli found in the sputum.

Much improved: Only slight objective symptoms remain. Patients subjectively quite well. Sputum may contain bacilli.

Somewhat improved: Subjective disturbance diminished. Objective symptoms somewhat reduced. Fever may continue.

Worse: Objective symptoms become noticeably worse after injection, or subjective symptoms seemed aggravated. These may not necessarily have been the direct result of the injection.

Necessary Precautions before Injection. As the toxicity of the remedy is very great it is absolutely necessary to have the patients under constant observation and control, and consequently they should be treated in hospitals only. Good results could never be obtained, we are sure, with ambulant treatment, for many serious and unexpected accidents may occur, especially when patients have a tendency to hemoptysis. In the case of patients suspected of intestinal tuberculosis, special attention should be paid to the evacuation of the bowels in order to avoid violent reaction. To secure complete and regular evacuations we used magnesium sulphuricum or some other like saline laxatives. Enemas were also used.

Treatment after the Injection. At first we required of all patients absolute rest for three days and nights after the injection, according to the instructions of Koga, but as this was sometimes quite unendurable, especially by those who had no very marked symptoms, we afterward changed the requirement to twenty-four hours of absolute rest, allowing them to sit up in bed during the following forty-eight hours at the time of meals and during urination and defecation. No ill effects followed this practice. This is only a general rule, however, and should be properly modified according to the condition of the individual patient. It is best to require during the three-day period, however, a half-fluid diet (rice mush), in order to avoid the irritating reaction in the bowels which very often takes place, especially in cases of intestinal tuberculosis or in patients who have chronic digestive disturbances.

Doses. The amount injected must, of course, be regulated according to the condition of the patients, but in general we used far smaller doses than those employed by Koga. At first we gave exactly as much as prescribed, but after some experience we found the dose too great and reduced it, and since then various unpleasant reactive phenomena, which formerly had been frequent, have usually been avoided. The doses which we used are as follows:

For patients in the first stage, 5 to 6.5 c.c.

For patients in the second stage, 3 to 4 c.c.

For patients in the third stage, 2 to 3 c.c.

Special attention was given to dosage in cases which gave a his-

tory of repeated or recent hemoptysis. In such cases, even if they were not much advanced, 2 to 3 c.c. were usually given as the first dose, and the amount given at further injections was determined in accordance with the observed effects of this amount. When suitable doses were found the same were kept constant for some time. We found that we had to be very cautious in using increasing doses of the drug, just as with tuberculin, in order to avoid such unpleasant events as hemoptysis, which may take place on the third to fifth injection. At any rate it is absolutely necessary to take into careful consideration the individual constitution and the stage of progress of the disease in each patient and having determined the most suitable dose to continue it throughout the treatment. If the chief symptoms have almost disappeared it is sometimes well to reduce the quantity in the two or three last injections. Otherwise the symptoms may be aggravated rather than entirely removed.

Local Reaction. According to Koga's report the local reaction is more or less noticeable after every injection. Dulness and rales may increase both in intensity and extent. This reaction is proportionate to the healing effect to some extent, *i. e.*, the greater the reaction the greater the healing effect. We first thought, therefore, that the reaction was a manifestation of the healing process, and that consequently that dose should be given which would cause some definite reaction. We found afterward, however, that the healing process and the reaction did not always go hand in hand, and that, on the contrary, the greatest healing effect was accompanied by the least reaction. Therefore we reduced the size of the doses so that the reaction might be avoided as nearly as possible.

As typical reactive symptoms we may count the follwoing signs: On the first or second day after the injection the increase of rales is more or less marked, accompanied by cough and expectoration. At first, when larger doses were given, this exaggeration of symptoms was present at almost every injection, but even at that time the increase of dulness was not always noted, as recorded in Koga's report. With the reduction of dosage this reaction is wanting in most cases. Sometimes the multiple rales, which persisted against all treatments, disappear at once, the dulness is wonderfully lessened, becoming somewhat tympanitic in tone, and the breath sounds become bronchial. These no doubt show that pneumonia-like changes are taking place. It is noteworthy that sometimes at the spot where dulness existed tympany appears and persists for one or two days while all other symptoms remain quite unchanged.

These reactive signs come out in a great majority of cases on the day after injection, and only in rarer cases on the second and third days. Sometimes they may occur only after from five to seven days, and in such cases the result seems generally to be bad. They

do not persist for more than two or three days and are removed usually by keeping the patients at rest without giving any special treatment. At times we obtained a marked sedative effect by the intravenous injection of calcium chloride, 5 per cent. solution. In general the reaction is more marked with large doses and more striking in the more advanced cases.

It is possible that the remedy may stimulate or arrest the process according to the severity of the disease perhaps or the size of the dose. But as there can be no reason that the same agent may have on the same organ or tissue at the same time two quite opposite effects so this apparent paradox should be explained. What seems to be inhibitive is not actually so, but the original effect is of a stimulating nature. When the dose is too small the effect of stimulation lasts for a very short time and soon runs into a period of arrest. Koga's assumption that the reaction itself is the manifestation of the healing process is supported by this explanation. It seems then that the secret of success with this treatment lies in choosing the most efficient dose, which varies with every individual. In this respect the remedy bears a great resemblance to tuberculin.

After the first period of stimulation, at the beginning of the period of arrest, all reactive symptoms become less marked, and the preëxisting dulness, rales, etc., are diminished in most cases. Especially is this true in relatively early cases, when dulness and rales disappear, expiration is no longer prolonged, and in areas in which the breath sounds had weakened or totally vanished, they may be heard again only after two or three successive injections. The disappearance of the dulness is most noteworthy. An effect so marked and so immediate has not been observed with any other remedy. In chronic cases, on the other hand, it is specially difficult to effect a total disappearance of the dulness.

We have avoided injecting patients who are suffering from early pleuritis, fearing that a violent reaction such as Koga described might possibly follow. In chronic cases of pleuritis, however, we have seen the pain and friction rub come out again, or the whole inflammatory process become active, accompanied by fever, pain, and renewed accumulation of exudation, etc. But this was found only in a few cases. In the great majority of cases no marked effect was observed.

Intestinal Tuberculosis. It is a well-known fact that cyan preparations possess great affinity for the bowels, and bleeding and submucous hemorrhage have often been observed in animals treated with cyan compounds. Clinical experience corresponds with these observations. Even if the bowel contents were carefully washed out as prescribed, and all possible means used to lessen the reaction, we found patients with intestinal tuberculosis who complained of uncomfortable feeling in the bowels, peristaltic unrest and pain, etc.,

after the injection. At Hamadera one patient discharged a bloody and mucous stool (dysenteric) after the injection. Recovery from this condition was very slow. These reactions may be avoided to a certain extent by evacuating the intestines, as emphatically recommended by Dr. Otani (chief of the clinical department of Kitasato Institute), and by giving smaller doses.

In one case of intestinal tuberculosis we saw a paroxysm of severe gastralgia after every injection, with no particular change in the stool. Another case of gastralgia came on a few hours after the injection in a patient who disobeyed our orders and ate an ordinary meal of boiled rice and some pieces of persimmons. As the patient had complained at two preceding injections of oppression of the stomach this attack of gastralgia may be explained as irritation caused by the injection and aggravated by the alimentary stimulation. The example goes to show how important it is to pay special attention to the diet. The same caution should be used in cases of simple bowel catarrh of acute or chronic nature. We saw several patients with chronic gastric catarrh, dilatation of the stomach, and gastroptosis who felt the stomach oppressed and filled up.

From the foregoing observations we conclude that attention to dosage, evacuation of bowels, and diet (fluid or semifluid diet is necessary) are particularly important in the treatment of patients suffering from intestinal tuberculosis or from general stomach or intestinal disturbances.

GLANDULAR TUBERCULOSIS. The remedy manifests a wonderful effect on relatively early cases of glandular tuberculosis. In cases of lymphoma colli tuberculosum the swollen glands are at first still more swollen and the skin at the point of swelling is reddened; but in a few days these signs diminish gradually, and by the time of the next injection the glands usually have become somewhat smaller than before the treatment was begun. After the next injection they are again swollen, but less extensively so, and as the symptoms abate the glands show further contraction. After several treatments the glands were almost wholly absorbed. A patient at Hamadera may be cited as an example of typical reaction to the treatment. The swollen glands, originally as large as an egg, were almost totally absorbed after six successive injections.

It is important to say here that a somewhat larger dosage is necessary in the treatment of glandular tuberculosis. A patient at Osaka who had a marked lesion in the right lung, which extended through two whole lobes and swollen glands as large as dove's eggs on both sides of the neck, showed a remarkable improvement after three injections, the following doses being given: 4 c.c. at the first injection, 5 c.c. at the second, and 6 c.c. at the third. The multiple rales were wonderfully reduced, dulness almost disappeared, fever descended, and the body weight increased, while not the slightest

influence could be detected on the swollen glands. After the fourth injection, when 7 c.c. were given, the glands became somewhat swollen, became painful to pressure, and were somewhat softened. On the fifth injection (6.5 c.c.), the same reactive signs were definitely noted, but as the pulmonary symptoms, which had practically disappeared, reappeared, the dose was reduced to 5 c.c., and this time no effect was observed. Since then, in spite of three successive injections, the glands remain quite unchanged. From this we may assume that it needs more than 6.5 c.c. to produce a beneficial effect upon glandular tuberculosis.

LARYNGEAL TUBERCULOSIS. Unfortunately the remedy seems to have very little effect on laryngeal tuberculosis.

GENERAL REACTIONS. *Fever.* The influence of the remedy upon fever varies very much, but in most afebrile cases without complication there is no rise in temperature. Occasionally a slight rise (0.5° C.) was observed, which disappeared usually on the following day. In slightly feverish cases the fever disappears in two or three days after injection. The temperature begins to rise before the next injection, which causes it again to fall. Repetition of the treatment brought a permanent afebrile condition after several injections. In favorable cases this result may be obtained by only one injection. We had little experience with highly feverish patients because we tried usually to bring the temperature down near normal, before beginning the treatment, by means of Ishigami's antituberculous serum, autovaccine cultivated from the sputum of the patient, or antipyretics. So far as our experience goes, however, the temperature is sooner or later brought down to normal or nearly so, though it does not fall immediately. In these cases we were particularly cautious about the size of the dose, for a large dose is quite likely to increase the fever, lower the general condition of nutrition, and bring on cachexia. We summarize the total results in febrile cases as follows:

AT TENNOJI.

Temperature.	1st stage.		2d stage.		3d stage.	
	Injections.	Per cent.	Injections.	Per cent.	Injections.	Per cent.
Raised . .	13	17.3	26	14.2	12	9.7
Lowered .	14	18.7	54	29.5	47	37.9
Unchanged .	48	64.0	103	56.3	65	52.4

AT HAMADERA.

Raised . .	21	26.9	66	18.0	27	16.9
Lowered .	11	14.2	55	15.0	60	37.7
Unchanged .	46	58.9	245	67.0	72	75.4

Pulse. No remarkable influence upon the bloodvessels was noted, though in not a few patients the rapidity of the pulse was somewhat reduced and the pulse became somewhat more regular. These phenomena are partly at least, attributable to the fact that the patient is always confined to bed and kept strictly at rest for a certain period.

Perspiration. In the great majority of cases we found the patients somewhat inclined to excessive perspiration. We recognized it in more than 50 per cent. of all patients.

AT TENNOJI.

	Number of patients.	Number of injections.	Number of patients sweated.	Number of injections after which sweating followed.	Percentage as to:	
					Patients.	Injections.
1st stage .	17	75	9	14	53.0	18.5
2d stage . .	36	183	20	36	55.5	19.7
3d stage . .	23	124	13	28	56.5	22.6
	76	382	42	70	55.3	20.6

AT HAMADERA.

1st stage .	21	78	2	3	9.5	3.8
2d stage . .	57	366	21	31	36.8	8.5
3d stage . .	29	109	19	28	65.5	16.5
	107	613	42	62	39.2	10.1

From this table it will be noticed that perspiration after the injection occurred much more frequently at Tennoji than at Hamadera. Especially is the difference noted in cases of the first stage. As our observations were made chiefly in summer, *i. e.*, from May to November, this result could be explained by the difference in temperature due to the respective locations of the two hospitals.[3]

Perspiration depends somewhat upon the dosage also. The greater the dose the more frequent the sweating. This relation may be clearly seen from the following table:

	Number of patients having frequent sweats.	Percentage.
Above 6.5 c.c.	40	53.2
Under 6.0 c.c.	5	6.5
Under 5.0 c.c.	10	13.0
Under 4.0 c.c.	11	14.3
Under 3.0 c.c.	10	13.0

[3] Hamadera is situated on the seashore about ten miles south of Osaka, and is popular as a summer resort because of its relatively cool climate. Tennoji Hospital is situated in the south suburb of Osaka, the greatest industrial city in Japan, and having a notoriously hot climate. The ventilation of the hospital is not ideal.

Perspiration also bears some relation to the number of injections. It is most frequently met with at the first injection and gradually disappears in the course of succeeding injections. This is shown in the following table:

AT TENNOJI.

	1st stage.	2d stage.	3d stage.	Total.	Percentage.
1st injection	7	18	11	36	46.1
2d "	4	6	8	18	23.0
3d "	2	6	4	12	15.4
4th "	1	4	1	6	7.7
5th "	0	1	1	2	2.6
6th "	0	0	1	1	1.3
7th "	0	1	1	2	2.6
8th "	0	0	0	0	0
9th "	0	0	1	1	1.3
10th "	0	0	0	0	0
11th "	0	0	0	0	0
Total	14	36	28	78	100.0

AT HAMADERA.

1st injection	2	13	10	28	40.3
2d "	1	6	8	15	24.3
3d "	0	7	3	10	16.1
4th "	0	1	3	4	6.5
5th "	0	1	2	3	4.8
6th "	0	0	1	1	1.6
7th "	0	1	0	1	1.6
8th "	0	1	0	1	1.6
9th "	0	1	0	1	1.6
10th "	0	0	1	1	1.6
11th "	0	0	0	0	0
Total	3	31	28	62	100.0

In general the perspiration occurs most often in cases of the third stage, but there are many exceptions to this rule.

ACCESSORY EFFECTS. The accessory ill effects of this remedy, which are met with only in rare cases, may be summarized as follows:

(*a*) Headache and congestion. In a small number of cases (2 to 6 per cent.), headache and congestion were complained of, accompanied by slight fever and flushing of the face. These signs remained only a few days.

(*b*) Oppressive feelings in the chest are often complained of by nervous and sensitive patients or when excessive dosage is applied. In most cases this symptom vanished within twenty-four hours, and it rarely lasted more than two or three days.

(*c*) Discomfort in stomach and intestines are felt by those who are suffering from intestinal tuberculosis or from acute or chronic digestive disturbances. This disappears after two or three days. Gastralgia was also noted in some cases.

GENERAL CONDITION AFTER INJECTION. *Subjective.* In many instances no remarkable change in subjective condition is noted. In not a few cases, however, the patient feels quite comfortable and at ease, as if he suddenly became quite free from the illness. This feeling is most common after the first injection, and by the third or fourth injection it is no longer noticed.

Changes in Nutrition. As already repeatedly described all patients are kept at rest for three days after injection, and during this period most of them lost some body weight. The patient was weighed on the day of injection, five days later, and not again until the next injection, two weeks later. We observed that on the fifth day the weight is somewhat reduced in most cases, and only in a small number of cases was it increased. On the day of the next injection, however, the loss is not only quite recovered, but often there is a definite increase in weight. There seems to be a direct relation between body weight and general improvement, *i. e.*, those who gain in body weight are usually much improved while those who lose weight are worse. Loss of weight was almost constant at first when larger doses were used. At that time even those who were strikingly improved lost weight and could not regain it by the time of the next injection. Since the reduction of dosage, however, increase of weight and general improvement run parallel.

We sum up the total results with regard to body weight in the following table:

AT TENNOJI.

	1st stage.	2d stage.	3d stage.	Total.
Weight increased:				
Number of patients	9	18	16	53
Percentage	52.9	77.8	69.6	66.8
Average increase per person	2.006 kg.	2.108 kg.	2.108 kg.	2.130 kg.
Weight decreased:				
Number of patients	8	8	7	23
Percentage	47.1	22.2	30.4	32.2
Average decrease per person	0.363 kg.	1.244 kg.	1.122 kg.	0.9 kg.
Weight constant	0	0	0	0
Maximum increase	5.4 kg.	6.4 kg.	4.35 kg.	
Maximum decrease	0.85 kg.	2.2 kg.	3.3 kg.	

AT HAMADERA.

Weight increased:				
Number of patients	18	44	20	82
Percentage	85.7	77.2	68.9	76.6
Average increase per person	1.811 kg.	2.645 kg.	2.355 kg.	2.391 kg.
Weight decreased:				
Number of patients	2	10	8	20
Percentage	9.5	17.6	27.6	18.7
Average decrease per person	0.9 kg.	1.22 kg.	2.355 kg.	1.643 kg.
Constant (percentage)	4.8	5.2	3.5	4.7
Maximum increase	6.4 kg.	13.2 kg.	5.5 kg.	
Maximum decrease	1.5 kg.	3.0 kg.	4.8 kg.	

It is easy to see from the table how remarkable the results are. It is to be noted that the results are in general better at Hamadera than at Tennoji. We may point out the following factors to explain the difference:

1. The climate in Hamadera is much better than in Tennoji.
2. The equipments are also much better at Hamadera.
3. The patients treated at Hamadera are usually from a class living under better social and economic conditions than those at Tennoji.
4. Patients stay much longer in the Sanatorium at Hamadera than at Tennoji.

We conclude therefore that although the favorable results of the treatment upon nutrition are remarkable, they cannot be attributed to the effect of the remedy alone. The open-air treatment, heliotherapy, hydrotherapy, dietetic treatment, and other routine treatments play an important part in the results.

Next to the increase in body weight, the improvement in the appearance is most remarkable. The anemic or cachectic and exhausted appearance which is so common in patients of advanced stages, with high fever, and especially in those suffering from intestinal tuberculosis, is in most cases wonderfully improved after several injections if the proper dosage has been chosen. The improvement in countenance may come before the restoration of nutrition and the disappearance of fever.

Cough and Expectoration. No remarkable change occurs on the day of injection. On the next day there is an increase of coughing and expectoration in many cases, followed by a gradual decrease. In some cases coughing and expectoration diminish immediately. There are some also in whom no change occurs.

Appetite. In patients suffering from gastro-intestinal disturbances the appetite is more or less affected, sometimes totally lost. This is rare, however, and in a great many cases the appetite remains almost or quite unaffected.

Lung Capacity. To measure the lung capacity we used Hutchinson's spirometer. This apparatus does not always give exact results. No definite conclusions can be drawn, therefore, and we use the measurements only as supplementary material. Results vary widely, showing no definite correspondence with other symptoms, yet in general there seems to be a favorable effect on lung capacity.

Laryngeal Tuberculosis. So far as our limited experience goes the remedy has a stimulating effect in laryngeal tuberculosis, that is, the surrounding parts of the ulcer become hyperemic and reddened for two or three days. Later the redness disappears, the surface becomes granulous in appearance, and the base of the ulcer is somewhat cleansed from caseous masses.

Intestinal Tuberculosis. Further experience is needed before any estimation can be made with regard to the therapeutic value of cyanocuprol for intestinal tuberculosis. As already mentioned the unfavorable reaction can be avoided in a measure if special attention is given to (1) dosage, (2) diet, (3) evacution of bowel contents. We treated several cases without causing reaction.

Influence upon Tubercle Bacilli. The results of the research vary very widely with respect to the change in number and form of tubercle bacilli in the sputum. We may classify the results as follows:

1. Immediately after the injection the number of bacilli is increased. Later it decreases and in favorable cases the bacilli disappear in a few days.
2. A gradual decrease in number of bacilli takes place without the initial increase.
3. In some cases when the examination of the sputum has been negative it becomes positive after one or two injections, and in the further course of the treatment it becomes again negative or remains positive continuously.
4. The bacilli at first disappear but are found again later.
5. No influence is observed.

We could confirm the facts reported by Koga in some cases, but the time of appearance of such forms as he found does not always bear the same relation to the time of injection. Moreover, such forms may often be seen in the sputa of chronic and cavernous cases. It is impossible, therefore, to decide whether or not such changes are actually caused by this treatment. On the other hand, we saw a patient in whom the sputum had been constantly negative suddenly spit out just after the third injection sputum containing numerous bacilli corresponding to No. X of Gaffky's table. The morphological changes had been noted more often before the reduction of dosage.

Provided the influence be a real one the question whether or not it is the direct effect of the preparation (in the sense of Ehrlich's chemotherapy) still requires investigation.

Hemoptysis. If proper dosage is given the danger of causing hemoptysis is not very great. At Tennoji, among 76 patients and 382 injections, we saw bloody sputum once only in each of 13 patients, and at Hamadera among 107 patients and 613 injections only once in each of 16 patients. The danger is somewhat greater when patients have a history of hemoptysis unless the injections are small and are not given too close to the time of hemoptysis.

At the time when we were still giving large doses, 7 c.c. and 7.5 c.c. were successively given to a patient who had expectorated blood once long before. The symptoms were so much improved that we gave him 8 c.c. at the next injection, attempting to kill all of the bacilli at one blow. On the day after injection, to our great astonish-

ment, the patient raised more than 300 c.c. of blood at one time, the general condition subsequently becoming much worse. The sputum continued bloody for more than a month, so that we were compelled to discontinue the treatment. This case was one of those which led us to the conclusion that the dose should be reduced even if the healing process was thereby retarded. There was a marked decrease in the number of occurrences of this sort after reduction of dosage, with no decided effect upon the efficacy of the drug. Since this bitter experience we have been particularly cautious in cases in which there is any history of hemoptysis. The period of rest is prolonged for such patients and narcotics are prescribed. The intravenous injection of calcium sometimes serves the purpose of a narcotic quite remarkably.

Relation to von Pirquet Reaction. At the spot where the von Pirquet inoculation had previously been made reddening becomes intense, induration increases in degree, and extension after the injection of cyanocuprol. The reaction becomes more intense with each successive injection until after the third to fifth, when the sensitiveness gradually decreases. It is noteworthy that in highly weakened cases, when the reaction ordinarily remains negative, it became positive after several injections.

Indication and Contra-indication. The relatively early cases, those in the first stage, are particularly indicated. Among patients of the second stage the treatment is indicated for those who have a slowly progressing limited lesion. If the affection is widespread or the change quite extensive, it requires great care to select suitable cases for the treatment.

Very much advanced cases, whose general condition is much weakened, or the breathing surface greatly restricted, are contra-indicated. Highly feverish cases, those in which the von Pirquet reaction is negative, or where there has been hemoptysis, are doubtful. Those who have advanced intestinal or laryngeal affections are unfitted for treatment. Patients suspected of general miliary tuberculosis or tuberculous meningitis are certainly contra-indicated. As for cases with recent pleuritis or peritonitis it is better to wait until the first inflammatory process is arrested.

Menstruation is not at all affected. We have no experience with pregnancy.

We very often combined a calcium salt with cyanocuprol to prevent hemoptysis or to prevent the reaction without apparent effect on the healing tendency of the latter. Five to ten c.c. of 5 per cent. solution of calcium chlorid is given intravenously.

Opsonin index is not in most cases increased after the injection.

The content of hemoglobin is increased after several injections.

The number of leukocytes is increased immediately after the injection, but after four to six days decreases again to the original number.

Better results with cyanocuprol are usually obtained in patients previously treated with tuberculotoxoidin.

SUMMARY. 1. Cyanocuprol is very effective in all cases of the first stage. In the majority of cases of the second stage it is also effective. With patients of the third stage it many manifest its effect to a certain extent if favorable cases are selected and proper dosage is given.

2. The effect of cyanocuprol cannot be called strictly chemotherapeutic. It shows in some respects a strong resemblance to tuberculin.

3. The essentials of the treatment with cyanocuprol lie in finding the proper dosage for each patient. If the individualization, which is especially important with this remedy, is properly carried out its value is indeed remarkable, surpassing all other remedies ever tried.

4. The combination of calcium prevents violent reactions and does not affect the efficacy of the drug.

5. The combination of immune therapy and sanatorium treatment is necessary.

6. The question of the duration of the treatment is an important one. According to our own experience if the patient is not improved after two or three injections, or is weakened, the dosage should be reduced or the interval extended. If this brings no improvement the treatement must be given up. Even in favorable cases, when the results are good after each injection, the treatment is best interrupted between the fifth and sixth and eleventh and twelfth injections, for at these times the condition is most improved. If treatment is continued in such cases there will be no benefit from it; instead there may be a return of previous symptoms and the patient's condition may become hopeless.

In conclusion, it is our pleasant duty to pay our best respects to Dr. Koga, and also to express our hearty thanks to Doctors Takagi, Imai, Yukawa, Honda, and Yano for their kind assistance throughout the whole period of our observations.

VAGINAL METASTASES OF HYPERNEPHROMA.

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THE urinary and genital apparatus in the female are closely connected both topographically and developmentally. In disease this intimate relationship becomes even more apparent. I need but mention the frequent occurrence of pyelitis in pregnancy, the effect upon the bladder of an incarcerated retroflexion of the gravid uterus, the role of cystocele in the etiology of genital prolapse, the relations

of the ureters to cancer of the cervix uteri, the question of vesical fistulæ, etc.

The case recorded below is an additional contribution to the borderland between gynecology and urology:

Mrs. Z., aged fifty-four years, referred by Dr. F. R. Fry, complained of severe and persistent pain in the abdomen due to the presence, in the left hypochondrium, of a large, hard and immovable tumor supposed to be retroperitoneal. She had lost thirty pounds in weight within the last few months. Her appetite was poor; the bowels were constipated. There had never been an attack of hematuria or of vesical disturbance.

An irritating and slightly offensive discharge from the vagina, brownish in color and doubly suspicious in a woman past the menopause, called for a vaginal examination. The exploring finger touched two round protuberances springing from the anterior vaginal wall immediately behind the introitus. One of these lay in the median line and the other directly behind it and a little to the right. The elevations were of the size and shape of raspberries, soft in consistency and connected with the vaginal wall by a broad base. Both were easily shelled out with the finger-nail, which procedure left a shallow and but slightly bleeding depression behind. The color of the small growths was grayish red. The rest of the genital system presented no abnormalities; the uterus and ovaries were in a state of physiological atrophy.

The microscopic examination (Dr. G. McConnell*) of the small growths revealed unexpected and highly interesting conditions. In one of them the stroma was made up of a basal layer of connective tissue (Fig. 1). From this sprang a freely anastomosing network of delicate connective-tissue fibers carrying capillaries (Fig. 2). In the peripheral portion such connective-tissue fibers could not be distinguished and the stroma was altogether formed of capillaries which, near the surface, were seen distended with blood. The anastomosing bloodvessels formed distinct alveoli, and these alveoli were densely filled with large polygonal and round cells whose nuclei were well stained. While the contours of the cells were well marked the protoplasm had not taken the stain. In many of the cells there were one or more vacuoles (fat droplets?) while in others a granular arrangement was discernible in the cell body. In some of the cells the nucleus was pushed to one side (Fig. 3). In the periphery of the growth there were several places of hemorrhagic infarct with necrosis of the tissue. In the deeper layers, near the basal connective-tissue wall, there was a reticulum of connective-tissue fibers within which small nests of the same polygonal cells were confined. Deposits of pigment were altogether absent.

* It is a pleasant obligation to thank Dr. McConnell, now in Waterloo, Iowa, for his valuable help.

FIG. 1.—Vaginal metastasis. A freely anastomosing network of delicate connective-tissue fibers forms alveoli which are filled with cells. Note the light color of the alveoli. Bausch & Lomb, 32 mm. Tessar.

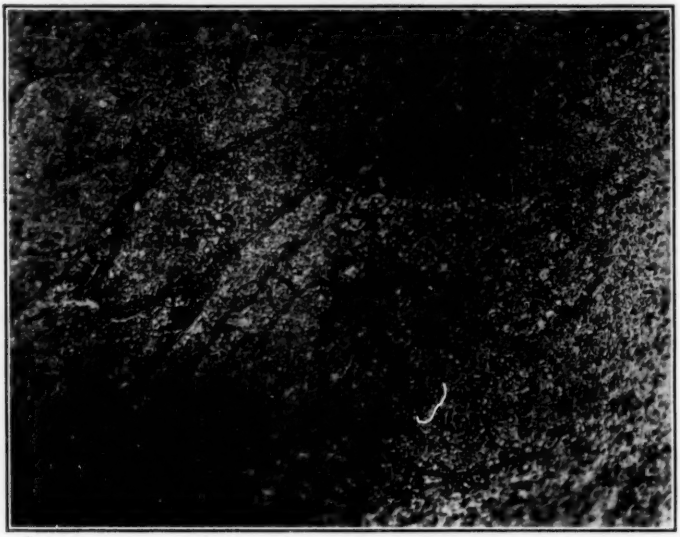

FIG. 2.—Alveoli in Fig. 1. enlarged. The connective-tissue septa carry capillaries. Bausch & Lomb, 16 mm. obj. 5 x ocul.

The microscopic picture of the second vaginal growth was somewhat different. The base was made up of a broad band of blood cells without any connective tissue. The contour of the tumor was round, with the exception of one indentation, and was, for the most part, covered with a very thin layer of epithelial cells derived, in all probability, from the mucous membrane of the vagina, and spread out over it like a decidua reflexa (Fig. 4). The stroma was formed by an excessively large number of tortuous and greatly engorged bloodvessels. The endothelial lining of these

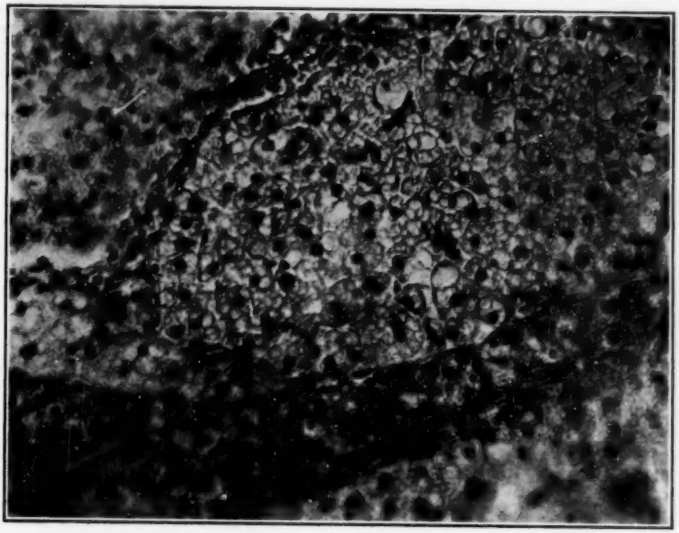

FIG. 3.—In the peripheral portion the alveoli are formed by capillaries. The alveoli are packed with large polygonal and round cells whose nuclei are well stained while the protoplasm has not taken the stain. Many of the cells are arranged in rows and are directly continuous with the endothelium of the bloodvessels without any intervening connective tissue. Note the vacuoles and eccentrically located cell nuclei. Bausch & Lomb, 4 mm. obj. 5 x ocul.

was plainly visible, but other constituents of the vessel walls were absent; connective tissue was discernible in the picture only in faint traces. The parenchyma between the bloodvessels was formed by the same large polygonal cells seen in the other growth. In certain places these cells formed solid columns. Vacuoles and granular arrangement within the cell bodies were also present, but neither pigment nor giant cells could be found. Extravasation of blood had occurred in a few places near the periphery. Round-cell infiltration was observed in two small areas beneath the vaginal covering.

While, thus, in the first picture the alveolar arrangement of the large polygonal cells predominated, the angiomatous condition of the bloodvessels was more conspicuous in the second growth. Both pictures, however, had so many features in common that they had to be considered as various types of one and the same condition.

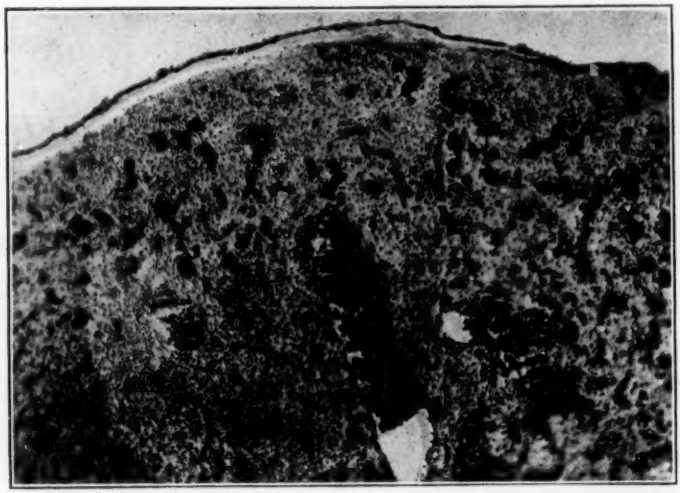

FIG. 4.—Periphery of second vaginal growth. The thin covering is derived from the vaginal mucosa. Note the abundance of tortuous and engorged bloodvessels and the light color of the parenchyma cells. Bausch & Lomb, 8 mm. obj. 5 x ocul.

Both tumors presented microscopically a peculiar glassy appearance, and from the resemblance of their structure to that of the adrenal glands they were interpreted as being hypernephromatous in nature and metastases of the large mass found previously in the left hypochondrium. This latter mass, therefore, was diagnosed as a hypernephroma of the kidney.

That this supposition was correct was proved at the sudden death of the patient three or four days after our diagnosis had been made. At the demand of the family, autopsy was restricted to the abdominal cavity and revealed the hypochondriac tumor to be a typical hypernephroma which had developed from the upper pole of the left kidney. The rest of the abdominal cavity was apparently free from metastases, and from our postmortem findings no definite cause of death could be determined. The two wounds in the vagina resulting from the enucleation of the metastatic growths had almost healed.

The kidney tumor had the size of a large man's fist.* Histologic-

* The tumor was exhibited at the International Surgical Congress in Brussels, but was lost on the way home.

ally, it presented the characteristic features of hypernephroma identical with those found in the vaginal growths. In addition, however, there were also papillary structures in which rows of polygonal cells were arranged along almost invisible capillaries, which in turn branched out from a central bloodvessel of a larger caliber. In several places these rows of cells, two or three deep, had a lumen in the center, caused perhaps by necrosis, thus forming a pseudoglandular arrangement. These gland-like structures were, however, easily distinguished from true glandular spaces which could be observed at about the middle of the microscopic field and were separated from the rest of the tumor by a capsule of connective tissue. We may assume that these glands belonged to the kidney proper and represented urinary tubules.

Epicrisis. Vaginal metastases of hypernephroma seem to be extremely rare. I have been able to find only the following nine instances of this sort in the literature at my disposal.

1. F. Henke[1] reports the case of a woman, aged sixty years, with multiple tumors of the vagina, which, at first, were thought to be metastases of uterine cancer. Besides, she had a pedunculated tumor of the skin of about the size of a goose egg and the shape of a mushroom. Postmortem revealed the presence of a typical malignant hypernephroma of the left kidney. This latter tumor as well as the growths in the skin and vagina contained a large amount of glycogen and presented identically the same microscopic picture. The cutaneous and vaginal tumors must therefore be considered as metastases of the suprarenal tumor.

2. A. von Rosthorn[2] demonstrated a vaginal metastasis of an "hemendothelioma" of the kidney. I was unable to find the original report. The name hemendothelioma, however, suggests that von Rosthorn presented his case at a time when the histogenesis of these tumors was still under discussion. Driessen,[3] Hildenbrand[4] and others believed that they originated from the endothelium of bloodvessels and lymphatics. As we shall see later the term "hypernephroma" has now been generally accepted, and Kelly[5] expressly states that this term includes the "endothelioma" of Driessen as well as the "angiosarcoma" of De Paoli, Beneke and Sudeck.

The case of von Rosthorn, however, is rather doubtful. Schottlaender[30] quite recently classified this case among those of "ectopic chorio-epithelioma."

3. Peham[6] speaks of a woman, aged fifty-nine years, who, for a few months, had complained of a bloody vaginal discharge; one and one-half years previously she had some urinary discomfort, and once there was an attack of hematuria. On examination a large hypernephroma of the left kidney was found. The anterior vaginal wall was infiltrated and a sessile growth the size of a hazelnut was discovered directly behind the introitus. The structure of this growth, on microscopic examination, was identical with that of the hypernephroma.

4. R. Freund[7] reports a vaginal metastasis in a woman, aged fifty-six years, which had appeared one and one-half years after the extirpation of the left kidney for "sarcoma." The metastatic growth had the size of a cherry; it was located upon the anterior vaginal wall to the left of the urethra, and had caused hemorrhages for the past six months. The microscopic examination of both the primary and metastatic tumors revealed typical hypernephroma.

5. Hoffmann[8] found in a woman, aged sixty-one years, a cauliflower growth in the vagina as a metastasis of a hypernephroma of the left kidney. There were numerous other metastases throughout the body.

6. Alban Doran[9] described in detail the findings in a woman, aged forty years, whose right kidney was extirpated for hypernephroma. Aside from metastases in the liver and lungs, there were several metastatic growths, both sessile and pedunculated, within the vagina.

7. In the discussion following Doran's paper, Overy[34] described a similar case in which a polypoid mass had been found attached to the anterior vaginal wall. This was removed and a large tumor in the right side of the abdomen was discovered. Two months later the vaginal growth had recurred and it was again removed. The patient died a month later. The postmortem examination showed that the abdominal tumor was primary and was a malignant adrenal tumor starting in an adrenal rest. There were numerous secondary deposits in the liver and lungs, sections of which showed more or less typical adrenal tissue.

8. Graefenberg[10] found, in a woman, aged fifty-four years, a tumor of the left kidney and two nodes of walnut and hazelnut size respectively upon the anterior and posterior vaginal walls immediately behind the introitus. Microscopic examination of these nodes revealed the picture of malignant hypernephroma. The vaginal growths obviously were metastases of the renal tumor.

9. Graefenberg[10] discovered, in a woman, aged sixty-five years, a deeply pigmented tumor of the vulva in the vicinity of the meatus urinarius. Microscopically the tumor showed the characteristics of hypernephroma, and upon autopsy, a malignant hypernephroma of the left kidney the size of a child's head was found. The growth in the vulva was the only metastasis of the renal tumor.

An interesting feature of my own case is the fact that the microscopic examination of the vaginal metastases enabled us to correctly diagnose the primary tumor. In like manner did Graefenberg[10] diagnosticate both his cases of hypernephroma from a histological examination of the secondary manifestations. Indeed, it is often only the metastasis which causes the patient to seek medical aid while the primary tumor, for the time being, produces no symptoms at all. Thus Hoffmann[11] found in a man who entered the hospital, because of pain in his leg, a metastasis in the femur which led him to

search for and find a hypernephroma of the kidney; and Israel[12] and Albrecht[13] likewise observed bone tumors which, after careful observation, were recognized as metastases of a hitherto obscure hypernephroma.

In my case the vaginal tumors, which from their proximity, may be considered as one, were clinically the only metastasis in the body; but as the autopsy had to be limited to the abdominal cavity the possibility of other metastases in the brain or thoracic cavity cannot definitely be excluded. Contrary to the opinion of Berg[31] there are but very few instances of solitary metastases of hypernephroma in literature. The case of Graefenberg[10] has already been referred to. In one of Albrecht's cases[13] a metastasis in the scapula was the only one in the body.

As a rule, however, hypernephroma causes multiple metastases. They are most frequently found in the bones and lungs, but since the disease is disseminated by way of the bloodvessels, almost all organs may become affected. Hoffmann[8] describes hypernephroma metastases in brain, liver, lungs, kidney, bronchial glands, various bones, the skin of the thigh and the vagina. Funccius[14] reports metastases in the ovary and pancreas, and Garceau[15] mentions, in addition, metastases in spleen, uterus, intestines, bladder and omentum. Harttung[33] recently recorded a metastasis in the spine.

In view of this multiplicity of metastasation in the various parts of the body the rarity of vaginal metastases is doubly remarkable. Graefenberg[10] endeavors to explain this phenomenon. He says that particles of the tumor usually enter the vena cava through the renal vein; thence they are carried through the heart into the pulmonary arteries. This, however, explains merely the frequency of metastasis in the lungs. According to Sutter's investigations, retrograde metastases of malignant kidney tumors may at times by disseminated throughout the entire genito-urinary apparatus by way of the vena spermatica. This possibility seems plausible in cases in which metastases are found in the ovaries, uterus and upper portions of the vagina for these localities are exposed to retrograde transportation of tumor particles by way of the spermatic vein through anastomoses with the plexus pampiniformis. This explanation, says Graefenberg, is, however, not sufficient for metastases in the lower portion of the vagina and the vulva. Tumor particles from the kidney can reach the vulva by way of the spermatic vein only if there is an anastomosis of the plexus pampiniformis with the obturator vein. Such an anastomosis exists at times. The obturator vein, again, receives rami pubici from the external genitals, and thus a direct com munication from the renal vein to the vulva is established. Since the left spermatic vein empties into the left renal vein, such a retrograde transportation of tumor particles to the external genitals seems more likely on this side than on the other because, under ordinary circumstances, the right spermatic vein does not empty into the renal vein but directly into the vena cava.

Graefenberg's contentions are borne out by the studies of Kownatzki[16] on the distribution of veins in the female pelvis. Kawnatzki depicts in Fig. 4 an old parametritis which has led to an anastomosis between the plexus pampiniformis and the obturator vein. He furthermore shows in his dissections that even without such an anomaly the pubic veins carry blood from the external genitals directly into the so-called median iliac vein which by means of the uterine veins is connected with the spermatic vein and thus with the renal vein.

The theoretical explanation of Graefenberg is supported by the fact that of the 10 hypernephromata here collected, 7 were on the left side. In 1 case the location of the tumor was not stated. In the case of Doran the hypernephroma was situated on the right side; the metastases were in the upper portion of the vagina and therefore do not come within the scope of this particular consideration. In Overy's case the exact location of the metastasis is not given. The preponderance of hypernephroma on the left side in these cases does not seem accidental. Keyes[17] says that renal growths are about equally frequent on the two sides, and Garceau[15] states: "The right side is a little more frequently affected than the left; 82 cases are recorded in which the disease occurred on the right, 77 on the left and in 17 the side was not stated." In contradistinction to these statistics, among which there are a number of individual observations, I find that the proportion is reversed if we consider whole series of cases reported by one and the same author, as in the following table:

Author.	Right.	Left.	Not stated.	Total.
Israel[12]	7	10	0	17
Kelly[8]	1	4	1	6
Albrecht[13]	9	19	0	28
Scudder[18]	2	3	1	6
	19	36	2	57

The diagnosis of hypernephromatous metastases in the vagina rests upon the microscopic examination. These metastases reproduce exactly in their minute structure the characteristics of the parent tumor (Garceau), and the latter, again, suggests histologically the structure of the cortex of the adrenal. It will be remembered that the adrenal gland is composed of a medullary and a cortical portion. The latter is subdivided into three more or less distinct layers, the *zona glomerulosa, zona fasciculata* and *zona reticularis*. In the case of tumor formation, however, these three layers are not evenly represented; the fascicular layer usually predominates. Moreover, as the tumor grows, atypical formation can occur, which may resemble adenoma, sarcoma, endothelioma, or carcinoma.[32] This variability of the microscopic picture has been the cause of much confusion until Lubarsch[19] and Birch-Hirschfeld[20] suggested

that an indifferent name should be chosen which would leave the question of histogenesis in abeyance and would merely signify that these tumors were derived from the adrenal. The name "hypernephroma" proposed by them has now been almost generally accepted.

That these tumors were of adrenal origin was first shown by Grawitz[21] in 1883, who, moreover, proved that the tumor formation did not so much take place in the adrenal proper as in "aberrant" adrenal tissue, which is so frequently found in the kidney. Such aberrant adrenal tissue was later demonstrated in all parts of the abdomen, but particularly in the urogenital tract, by Imbert, Schmorl,[22] Marchand, Chiari, Hanau, Ulrich, Targett,[23] Aichel,[24] Pick,[25] and numerous others. Consequently, primary hypernephromata originating from these so-called adrenal rests have been observed in organs other than the kidneys. Thus, Keen, Pfahler and Ellis,[26] in a collection of 163 cases, found 157 in the kidney, 3 in the adrenal, 2 in the liver and 1 in the uterus. Pick[24] and Bovin[27] described primary hypernephroma in the ovary and Weiss[28] a like tumor in the broad ligament.

Although usually of slow growth, hypernephroma is potentially a malignant tumor, and metastasation will occur sooner or later. These metastases are almost always multiple, as mentioned above, and their presence contra-indicates any operation.

To return now to vaginal metastases with which we are here more particularly concerned, they are of considerable practical importance to the gynecologist. As Freund[7] justly points out, metrorrhagias or a bloody vaginal discharge, after a previous nephrectomy, should make us think of metastases of hypernephroma, particularly if the anterior vaginal wall near the introitus is affected.

Malignant tumors of the vagina are usually considered primary. It seems but reasonable to think that in some such cases the tumor is in reality a metastasis (Veit[29]). If more attention would be given to this point in future the bad prognosis of malignant new growth of the vagina would, to a certain extent at least, be explained. It is not at all illogical to surmise that many a supposed sarcoma or carcinoma of the vagina will, on careful microscopic examination, prove to be hypernephromatous in nature and that a thorough investigation will lead to the discovery of the tumor in the kidney.

SUMMARY. In a woman, aged fifty-four years, a large retroperitoneal tumor on the left side was found whose nature could not be determined. Vaginal examination revealed the presence of two growths in the anterior vaginal wall near the introitus. These growths were of the size and shape of raspberries and were easily shelled out with the finger-nail. Microscopic examination showed typical hypernephroma. It was then assumed that the two vaginal growths were metastases of the obscure retroperitoneal tumor and that the latter was a hypernephroma of the kidney. The patient

died suddenly a few days later and autopsy fully confirmed the correctness of the diagnosis.

Vaginal metastases of hypernephroma are extremely rare. Literature contains but 9 other instances of this kind. It is, however, probable that many cases of primary sarcoma of the vagina are in reality hypernephromatous in nature and secondary to a malignant tumor of the kidney.

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A REPORT OF THIRTY CASES OF MENINGOCOCCIC CEREBROSPINAL MENINGITIS.

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BELIEVING that a discussion of the clinical aspects of cerebrospinal meningitis might be of some value, we report a series of 30 cases that have been admitted and treated in the Base Hospital, Camp Pike, Arkansas, during November and December, 1917.

In the majority of instances the cases have been admitted within twelve to forty-eight hours after the appearance of symptoms, but a few were practically moribund at that time and died within a comparatively few hours. These, however, are included in the report.

For various reasons the meningitis patients have been turned over to the laboratory department, not only as regards diagnosis, but also treatment, a ward in the hospital being set aside for that purpose. The greatest part of the work has been done by Captain Morris and a much smaller amount by Captain Seehorn and Major McConnell.

Symptoms on Admission. Although several of the patients were unconscious on admission, it was possible, as a rule, to elicit definite information concerning the subjective symptoms. In order of frequency they were as follows: (1) profound frontal headache; (2) stupor or coma; (3) rigidity of the neck; (4) vomiting; (5) Kernig's sign; (6) increased knee-jerks; (7) hyperesthesia; (8) slow pulse; (9) petechiæ; (10) slight increase in temperature. Strabismus was not present as an early symptom.

Headache. The headache was very severe in character, being much more marked than in typhoid fever, and nearly always was frontal. In one case in which it became basilar the patient lapsed into coma and finally died.

Mental Condition. In regard to the mental condition, there were all variations from an almost abnormal acuteness to complete coma. As a rule the patient was dull and inclined to sleep, but could be aroused, at which times he would appear irritable. Otherwise he would remain quiet, and breathing would be of a normal type, quite unlike that of the alcoholic, uremic or apoplectic.

Rigidity of the neck was, as a rule, well marked and accompanied by more or less retraction. In some instances this reached the point of a mild degree of opisthotonos. Any attempt at flexion, either active or passive, was painful, and evidently this rigidity was in no way due to the will of the patient. In this respect it differs from that seen in poliomyelitis, as in the latter the patient voluntarily resists, knowing that any motion will be painful. If this stiffness is not noticeable early it soon becomes very evident.

Vomiting occurred in about two-thirds of the cases and was of the projectile or cerebral type, coming without warning and without previous nausea. In a few of the cases it was the initial symptom.

Kernig's sign was positive in nearly every case, either slight or well marked, according to the general condition of the patient; but as it is found in various other infections, it is not of great diagnostic value. It was noted, however, that just at the moment when knee extension was made, after full flexion of the hip, both pupils dilate promptly and markedly. This same phenomenon was noted when flexion of the neck was attempted.

The knee-jerks were exaggerated in most of the cases, as were the plantar reflexes. Babinski's sign was absent in practically every case.

Hyperesthesia was present in many instances to a high degree and at times the skin showed marked irritability, as evidenced by positive "tâche cérébrale."

The pulse in nearly every case was slow, commonly between sixty and seventy, and not unusually it was in the fifties; as a rule a full volume, but occasionally irregular or intermittent, or both. The rate seemed to have little relation to the degree of temperature.

Petechiæ were present in but a small percentage of the cases, being marked in but three. Generally the distribution was diffuse, with variations in size and shape and not disappearing on pressure. In those showing well-marked petechiæ the other symptoms were severe, including a markedly purulent cerebrospinal fluid occurring in large amount, with a great increase in globulin.

Temperature. The temperature has not been high, particularly early in the disease. On admission the temperature was, as a rule, less than 101°, and even some of the worst cases did not go over 100.5°. The highest that was noted was 104.5°. except in one case in which it went up to 107° shortly before death. As compared with the English report the average temperature at the time of admission in our series was distinctly lower.

Various other symptoms were noted but did not appear with sufficient regularity to make them of diagnostic importance.

Strabismus of the convergent type was rather frequent.

Deafness was usually mild, but at times was well marked, was quite common, and generally persisted for a longer time than did the strabismus.

Herpes appeared in practically all of the cases and were abundant, usually most extensive on the lips at the mucocutaneous junction. The ears, nose and forehead were involved also. In several patients the herpes were so extreme that a good part of the face was covered by large scabs and the nose or an ear was swollen to twice its normal size.

The procedure in the cases was as follows: When the patient was admitted to the hospital he was seen by the medical officer, and if meningitis were suspected the laboratory was notified. A physical examination was made, and if it were decided to make a lumbar puncture the patient was sent to the meningitis ward. The skin over the junction of the fourth and fifth or third and fourth lumbar vertebræ was painted with iodin and a puncture made. If the patient were unconscious no anesthetic was used, as a rule. If slightly conscious and restless a mild chloroform anesthesia was employed. If fully conscious the patient was told what was to be done and no anesthetic was given. As a rule, general anesthesia was not used, as there seemed to be very little difficulty in removing considerable quantities of fluid, in one case as much as 125 c.c. On removing the stylet from the needle the first part of the fluid was allowed to flow into a sterile test-tube, then a small amount into a tube of culture media (serum dextrose agar). If the fluid were turbid the canal was allowed to drain and a dose of antimeningitis serum injected at once, the diagnosis being made later. It has happened in three instances that the cause of the condition was found to be the pneumococcus. These are not included in this series. Irrespective of the total amount of fluid removed, provided that it was more than 45 c.c., there was injected immediately 40 c.c. of serum. Whenever the quantity obtained was less than 45 c.c. the rule of injecting an amount of serum 5 c.c. less than that of the fluid withdrawn was followed.

If the spinal fluid were clear a globulin test and a cell count was made.

If either or both of these indicated a spinal irritation a dose of serum was given.

In regard to the pressure under which the fluid flowed it was observed that practically all the cases showed an increase, either moderate or marked. Inasmuch as an increased pressure was found in a number of cases that proved to be negative, this condition was disregarded as a positive indication for the injection of serum. Reliance was placed upon the character of the fluid, the presence of globulin and the cell count. The spinal fluid was centrifuged and the diagnosis confirmed by finding an abundance of polymorphonuclear leukocytes and a Gram-negative diplococcus. A positive diagnosis was made from the cultures on the basis of the appearance of the colonies and the finding of Gram-negative diplococci. Agglutination was not resorted to to determine the type of the organism on account of lack of personnel and of material. The fact that the cases with but very few exceptions showed improvement following the first injection of the antimeningitis serum would seem to indicate the correctness of the diagnosis.

In the examination of the sediment obtained by centrifuging the cerebrospinal fluid the organisms show the general morphology of the meningococcus. There was, at times, considerable variation in the size, shape and position in regard to the polymorphonuclear leukocytes. Most of the cocci were large "biscuit" shaped, arranged in pairs, as a rule, but sometimes like tetracocci. Others were smaller and more rounded. They were found both extra- and intracellularly, as has been reported by many investigators. Consequently not much weight was attached to location. Many appeared to be within the nuclei of the leukocytes. The organisms were uniformly Gram-negative. The number present varied greatly, some cases containing thousands, while in others, apparently of equal severity, it was with the greatest difficulty that any could be demonstrated. It was noted, as has been reported by the English Commission, that after the first injection the organisms were greatly diminished in those cases in which they had been numerous, and that after the second or third injection they could not be demonstrated.

In the more severe cases, when the fluid was allowed to stand for a short time, a diffuse gelatinous coagulum formed, this eventually settling to the bottom of the test-tube. The coagulum was very tenacious and could not be removed piecemeal. The uncoagulated part of the fluid remained cloudy, and on being centrifuged, pus cells and meningococci could be demonstrated.

Administration of Serum. In giving the serum the gravity method was not employed. Instead a Luer syringe of 40 c.c. capacity was used, there being a rubber tube with nipples for connection with the syringe and the needle. The serum was injected very slowly, but in many instances gave rise to more or less severe cramp-like pains in the lower extremities; these, however, were only temporary and did not require any treatment. It was very seldom that any untoward symptoms developed, the respirations continued without interruption and the pulse did not become rapid or weak. No attempts were made to follow Sophian's scheme of taking the blood-pressure at the time of injection.

In giving subsequent treatments the same methods were used and as

much fluid as would readily flow was removed. The amount obtained varied greatly, the maximum amount being 150 c.c. and the minimum 5 c.c. Both these cases resulted fatally.

Amount of Serum Given and Frequency of Injections. All of the cases, as soon as the lumbar puncture was done, and either a cloudy fluid discovered or a positive globulin obtained, were given, as a rule, 40 c.c. of serum. As already stated, the dose depending upon the amount of fluid withdrawn, in most instances the initial puncture yielded upward of 50 c.c. According to our experience it would appear unnecessary to give the serum more frequently than at twenty-four-hour intervals excepting in those fulminating forms when death seems imminent. One patient received four injections within thirty-six hours and showed improvement after each treatment. With but two or three exceptions the first three injections were given at twenty-four-hour intervals. The period between treatments was increased only when the temperature had been down to normal for at least thirty-six hours and when the last puncture had yielded a fluid decidedly less turbid than that obtained at the initial puncture. The globulin reaction (Noguchi method) also was used as a guide as to the time interval and prognosis. As the fluid became less turbid the globulin diminished relatively. Thus from a four-plus reaction at the first it would diminish, as a rule, so that by the third lumbar puncture the reaction would be one plus or less. Consequently, when the fluid decreased in turbidity, regardless of the amount obtained when the temperature had been normal for a minimum of thirty-six hours and when the globulin reaction came down to one plus or less, it seemed safe to wait forty-eight hours or perhaps longer before another injection was given. This depended, of course, as to whether or not any disturbing symptoms made their appearance.

Regarding the globulin reaction it was noted that the patient occasionally showed a marked improvement, yet the globulin did not go below two plus. At such times it is safe to disregard the globulin and wait forty-eight hours before treating. The persistence of the reaction may be due to the irritation of the serum or to the puncture itself.

Many of the cases will need no further serum after the fourth dose, yet it may be well to make a puncture at the end of forty-eight or seventy-two hours later to determine the pressure, the quality and quantity of the fluid and the globulin reaction. It might be recommended that in spite of the above findings being negative the patient be given another dose. In this connection it was observed that if after an interval of forty-eight or seventy-two hours another dose is given to a case that shows apparent recovery a violent reaction may occur. This reaction is far more severe than that following any previous injection. The temperature rises abruptly, the pulse increases markedly in rapidity and is occasionally irregular, pain in the back becomes acute and even a wild delirium has occurred. These symptoms subsided in from twelve to eighteen hours without any unpleasant sequelæ. In spite of the possibility of such a reaction it has been deemed advisable to give the additional injection.

If the patient does not show improvement it may be necessary to continue the lumbar punctures until recovery or death ensues. In one case, which finally proved fatal, twenty-three lumbar punctures were made.

The daily course of the disease showed interesting changes. Many of the patients were admitted, in a semicomatose condition that made it impossible to get any very clear statements. For that reason it was generally an easy matter to determine the effect of the serum by noting whether there was or was not any decrease in the stupor. Practically all of these cases showed signs of returning consciousness within six hours after the first injection. Within twelve hours nearly all could tell clearly events which took place up to the time of becoming unconscious, occasionally remembering some trivial occurrence during the period of coma. This happened even in four of the fatal cases.

The following signs of improvement were considered of value in the order given, and on them was based the prognosis of the case: (1) improvement in the consciousness of the patient; (2) fall in temperature to nearly normal; (3) diminution in intensity of headache; (4) no decrease or marked increase in the pulse rate; (5) no increase in the rigidity of the neck; (6) decrease in the globulin. It would seem that the early signs of improvement, those appearing within six hours after the first injection of the serum, are due, in part, to the fall of intracranial pressure, following the withdrawal of the large amount of cerebrospinal fluid. For this reason it does not seem advisable to base a favorable prognosis on very early improvement. If, however, the above-mentioned signs are still present at the end of twenty-four hours the probabilities are that the disease is yielding to the treatment. It must be remembered though that this form of cerebrospinal meningitis is a very capricious disease and must be watched carefully. If these indications of betterment were still present after twenty-four hours the improvement continued almost miraculously and with progressive rapidity. The favorable cases, by the end of thirty-six hours, became entirely conscious and were interested in what was being done for them. After this stage the temperature rarely rose above 101° and in most instances went no higher than 100°. All temperatures were rectal. The headache disappeared but the patients still had very vivid recollections of its terrific intensity. The pulse rate was usually about the same as on admission, or very slightly increased, generally of good quality and regular. Some of the cases, however, on admission had intermittent and irregular pulses. By this time the stiffness of the neck was less marked and the excruciating pain formerly present when attempts at flexion were made was absent. Some of the patients, even at this early stage, had complete lateral motion, with a fair degree of flexion.

As the favorable course continued it was within three to five days that most of the cases felt practically normal, except for a feeling of weakness, of which they all complained. This was most marked in the back and neck, probably due to the fact that the muscles of these regions had been contracted spasmodically for so long that more or less of the muscular tonicity had been lost.

The well-known observation that in practically all fevers an ascending pulse with a descending temperature is of bad prognostic import was emphasized in this series of meningitis. This was demonstrated very clearly in one of the fatal cases. He at first seemed to be doing as well as the others, yet his pulse rate increased progressively while his temperature decreased. He received twenty-three intraspinous inoculations of serum. This case terminated fatally.

No.	Initials.	Stage when treatment was begun. Approximate.	Number of lumbar punctures.	Amount of serum given.	Complications.	Period to convalescence or death.
1	J. O.	24 hours	7	205 c.c.	None	Oct. 31 to Nov. 7; cured.
2	J. F.	24 hours	11	320 c.c.	None	Nov. 8 to Nov. 18; cured.
3	J. V.	At least 18 hours	23	695 c.c.	None	Nov. 9 to Dec. 6; died.
4	F. F.	Admitted Oct. 29 Treated Nov. 11	16	440 c.c.	Broncho-pneumonia	27 days; died.
5	J. B.	24 hours	6	150 c.c.	None	Nov. 11 to Nov. 16; cured.
6	A. McM.	24 hours	23	555 c.c.	None	Nov. 11 to Dec. 8; cured.
7	H. D.	36 hours	5	125 c.c.	None	Nov. 12 to Nov. 15; cured.
8	F. J.	24 hours	6	155 c.c.	Orchitis	Nov. 13 to Nov. 20; cured.
9	G. M.	36 hours	7	110 c.c.	None	Nov. 15 to Nov. 29; cured.
10	F. S.	40 hours	10	210 c.c.	Orchitis	Nov. 16 to Dec. 11; cured.
11	L. D.	At least 24 hours	17	440 c.c.	Esophageal spasm	19 days; died.
12	M. H.	48 hours	15	345 c.c.	Esophageal spasm	Nov. 20 to Dec. 4; cured.
13	P. W.	24 hours	4	120 c.c.	None	Nov. 20 to Nov. 23; cured.
14	O. D.	48 hours	11	345 c.c.	None	Nov. 24 to Dec. 4; cured.
15	W. R.	5 days	1	40 c.c.	None	6 days; died.
16	J. T.	72 hours	5	120 c.c.	None	Dec. 3 to Dec. 8; cured.
17	G. S.	Over a week; low grade	4	105 c.c.	None	Dec. 2 to Dec. 8; cured.
18	A. W.	36 hours	8	200 c.c.	None	Dec. 4 to Dec. 12; cured.
19	C. M.	24 hours	4	110 c.c.	None	Dec. 7 to Dec. 10; cured.
20	J. H.	36 hours	5	120 c.c.	None	Dec. 9 to Dec. 16; cured.
21	W. B.	72 hours	4	140 c.c.	None	Dec. 14 to Dec. 17; cured.
22	R. P.	48 hours	1	40 c.c.	Anaphylaxis	Few hours; died.
23	R. W.	48 hours	5	135 c.c.	None	Dec. 16 to Dec. 20; cured.
24	M. J.	24 hours	5	110 c.c.	None	Dec. 18 to Dec. 22; cured.
25	J. S.	24 hours	3	90 c.c.	None	Dec. 20 to Dec. 22; cured.
26	W. C.	24 hours	3	75 c.c.	None	Dec. 20 to Dec. 22; cured.
27	W. R.	48 hours	2	40 c.c.	None	Dec. 23 to Dec. 25; died.
28	H. G.	24 hours	14	340 c.c.	None	Dec. 25 to Jan. 9; died.
29	C. H.	24 hours	5	140 c.c.	None	Dec. 25 to Jan. 1; cured.
30	A. W	24 hours	4	120 c.c.	None	Dec. 29 to Jan. 1; cured.

Complications. There were but two complications that made their appearance, orchitis and esophageal spasm. Orchitis occurred in two instances, one being unilateral and the other bilateral. The testicle involved was enlarged, and was extremely painful and tender. The epididymis, however, was not attacked. The process subsided under rest and the application of ice-caps. A venereal history was denied by both patients, and in neither were there any indications of any past or present trouble. In addition the absence of involvement of the epididymis would seem to favor the non-venereal character of the orchitis.

The other complication also appeared in 2 of the cases, both of which complained of difficulty in swallowing even liquids. In one of them the spasm cleared up very shortly without any special treatment. In the other the spasm persisted and attempts to feed by means of the stomach-tube were made. The first feeding was successful, but after that it became impossible to pass the tube into the stomach even under chloroform anesthesia. The tube would traverse about three inches of the esophagus, beyond which point it would not pass and would begin to coil upon itself. After several attempts were made a gastrostomy was performed. Twelve hours later the patient died, more from asthenia due to lack of nourishment than from the result of the operation or from marked pathological changes, due to the meningitis. Rectal feeding had been tried, but nothing was retained.

In addition to the above-mentioned complications certain other conditions developed in the course of the disease. The most common were serum sickness and urticaria. Most of the cases developed an urticaria in from seven to ten days after the first serum injection. In seeking for a cause for this late occurrence the conclusion was reached that the repeated intraspinous injections of serum gradually increase the permeability of the choroid plexus so as to allow the passage of the serum into the blood stream. That this process takes place on an extensive scale is evidenced by the fact that the urticaria produced is widespread and abundant. In this respect the action is interesting when compared with that of the intravenous injections of salvarsan, as with that there is very little, if any, passage of arsenic into the cerebrospinal fluid. Some of the herpes developed upon the urticarial wheals and thus produced a peculiar eruption.

So was stated in the British report, and as has been our experience, no symptoms of acute anaphylaxis have developed; the urticaria has been the only indication of active serum sickness. In one instance there was a very unfortunate occurrence. This patient was admitted in a moribund condition with his body covered by a diffuse petechial rash. He was given 40 c.c. of antimeningococcus serum immediately upon the removal of the spinal fluid. Three hours later it was decided, on account of the evident severity of the case, to give some serum intravenously. Forty cubic centimeters were given and within a few minutes after the withdrawal of the needle an acute superficial edema appeared, most noticeable in the eyelids, which rapidly became swollen, and within fifteen minutes the patient died from respiratory failure. At the time that it was decided to give the intravenous injection the question of anaphylaxis was considered, but in view of the fact that 40 c.c. of serum had been given intraspinously three hours before, without any disturbances occurring, it was decided to give the serum intravenously. This result substantiates the belief that it is not until repeated injections have been given that the choroid plexus becomes permeable.

So far as the autopsy reports are concerned there was comparatively little found; the findings were as follows:

Case I.—J. J. V. Purulent meningitis, chiefly basilar, but some slight general involvement. Lateral ventricles contained an increased amount of fluid, quite turbid in appearance. Large amount of cerebrospinal fluid. Scattered areas of bronchopneumonia of right lower lobe, with slight purulent pleuritis. Pneumococci found in smear from pleura.

Case II.—F. F., purulent meningitis. Large amount of fluid present. A few areas of purulent exudate over the frontal lobes. Fluid in ventricles slightly increased and cloudy. Bronchopneumonia and edema of both lungs, particularly the lower lobes. Small amount of slightly turbid fluid in the pericardium. Parenchymatous changes in the kidneys.

Case III.—L. D. Basilar meningitis. Congestion and edema of both lungs.

Although this series does not comprise very many cases, yet the study of them has been of the greatest interest. The chief factor in regard to the prognosis is the period at which the treatment is begun. Under the conditions of civil life these cases are more likely to remain under

observation for a day or two before the diagnosis is made and treatment instituted. At present when the probabilities of a case being meningitis are very great the cases come to the hospital much earlier. In fact, the suspected cases have outnumbered the true. The principle followed has been that it is much better to make a lumbar puncture and get negative results than to overlook a case. A number of patients showing well-marked symptoms of meningeal irritation have proved negative so far as meningitis is concerned, but several on further examination have shown the presence of pneumonia.

The treatment has been instituted in practically all the cases, just on the gross appearance of the fluid without waiting for any further confirmation of the diagnosis. It has also been evident that the conditions of the patient at the time of admission was not always a reliable ground on which to base the prognosis. Some of those who were in well-marked coma came out more rapidly and returned to normal more quickly than others who at first seemed less severely attacked.

As has been the experience generally, those who have recovered after receiving the serum treatment have remained entirely free from any sequelæ. Those who have been discharged as cured have not had a trace of any trouble, no interference with vision or hearing, nothing other than the general weakness following any severe disease.

In regard to the source of infection very little, in a way, has been determined. Eleven of the cases were received from two companies of two regiments that came to the cantonment from an infected section. In about a month it was apparently quiescent in these troops, then after a period of ten days another case developed, but for the past month there have been no further cases. Other cases were much more sporadic, coming from various regiments and companies scattered all around the Camp. In the case occurring in a nurse it was found that she had been taking care of a patient who subsequently developed meningitis. It is interesting to note, however, that both she and the patient developed the disease at practically the same time.

In conclusion it would seem that the important points are:

1. Early diagnosis.
2. Prompt treatment.
3. Persistent treatment.
4. Symptomatic treatment. Control of convulsions by bromides and chloral. Heart stimulants such as digitalein, strychnin and atropin also were used.

AMERICAN JOURNAL OF CARE FOR CRIPPLES.

THE current number of the *American Journal of Care for Cripples* maintains the level of war interest established by its predecessors since inauguration of the policy to include consideration of the military phases of the subject with which it deals.

THE FRENCH SYSTEM FOR RETURN TO CIVILIAN LIFE OF CRIPPLED AND DISCHARGED SOLDIERS. An important and substantial contribution in this issue is that by Major John L. Todd, C. A. M. C., under the above title. Major Todd takes pains to emphasize that the information at his disposal has been obtained from men or commissions

entrusted with such work rather than from the titular heads of departments and considers at some length the methods followed by the French in returning the men discharged from the army to civilian life. He emphasizes also that these methods have by no means reached a final form and are divided in general into the following stages:

1. Active medical and surgical treatment.
2. Functional reëducation.
3. The provision of artificial appliances.
4. Professional reëducation.
5. Establishment in civilian life.

It seems that, for military purposes, the French territory is divided into twenty-one regions, each having an organization complete in itself, and this general structure forms the basis of arrangements for the return of soldiers to their homes. It is estimated that about 30 to 40 per cent. of the French Army will at some time or other be admitted to hospitals established under this plan because of wounds or disease. In addition to general hospitals and those intended for particular purposes the greatest importance is attached to the orthopedic centers, of which there is one in each of the above army regions.

Major Todd's article makes no attempt to consider medical or surgical matters in details, but a few interesting statements are made such as that to the effect that in the orthopedic hospitals above mentioned the stump of every patient having suffered amputation is radiographed on admission. By these means exostoses have been found to be very frequent, especially in the femur often causing a painful stump. It has been found inadvisable to remove them at once because of the possibility of lighting up an otherwise dormant infection by such activities.

Proceeding to the topic of Functional Reëducation, Major Todd places brief emphasis upon the fact that work properly selected and graduated, has not only a high psychic value in men of lowered morale, but also constitutes the best possible means of reaccustoming muscles to action. Incidentally he remarks that many of the nurses and volunteers giving massage and other treatments to such patients have little technical knowledge and that steps are being taken to remedy this by proper instruction.

Under Artificial Appliances the point is brought out that for purposes of uniformity these are to be issued at only six centers in France, together with the admission that the modern aim of an artificial appliance should be to remedy the physiological and not the anatomical loss. Interestingly enough one of the best wooden legs examined by the commission was made for himself by a young joiner and advantage is taken of individual inventiveness and experience in such instances.

It is the intention in France that each man who has suffered amputation shall be eventually supplied with two artificial limbs, one to be held in reserve and it is also noteworthy that laboratories and workshops have been established, not only for the manufacture but also for the devising of artificial appliances, such as those, for example, at Bordeaux and Lyons.

Major Todd proceeds to the other component phases of his large topic and calls attention to the importance of the selection of suitable occupation for disabled men, emphasizing that such choice must not be lightly made, as the "mutilé" is not always capable of deciding

properly. Considerable space is devoted to a survey of this field, including consideration of the blind and deaf. Establishment in civil life is also considered, and Major Todd makes the interesting statement that large numbers of men are being trained as manufacturing orthopedists at the centers of reëducation, and further states that it is well that this is so because already, ironically enough, German manufacturers of artificial limbs are sending out circulars to obtain business in France. The author believes that the many industries under way and planned will do away with the long-established necessity for Old Soldiers' Homes after the war is over, although there will inevitably be a small number of discharged soldiers receiving pensions but incapable of looking after themselves entirely.

Pensions and insurance are taken up in detail, which need not figure in this review, together with the means necessary to meet them. An interesting section is that on Tuberculosis. From a military point of view a soldier is deemed unfit for service when discovered to be tubercular. Although it is plainly the desire of the administration that rulings in this connection shall be liberally interpreted, it is clear that the State should be held liable for disease only in proportion as that disease is demonstrably due to service. There is obviously room for injustice in carrying out such intentions, and tubercular soldiers are usually discharged without a pension.

To date thirteen so-called sanitary stations have been established and twelve more are about to be opened, with the expectation that about 10,000 patients can thus be cared for yearly. The object of these sanitary stations is not to treat tuberculosis but to teach patients how to live so as to avoid infecting others. The duty of caring for these dependents will fall upon the civil and not the military power, and from the nature of their functions most of these sanitary stations will disappear soon after the war's end.

Major Todd remarks that although Germany has forbidden publications concerning prosthesis and functional reëducation, nevertheless considerable information has leaked out and is available to students of the subject.

Another interesting caption in the present article is that devoted to the French nursing system. It seems that before 1903 nine-tenths of the French nursing was done by nuns, and while the school established for this purpose at Salpêtrière, upon Governmental disruption of religious congregations, produced many good nurses, some were not of the desirable type. It appears that the number of highly trained professional nurses in France is less than that now available in Canada, but, on the other hand, the number of women having received some training is considerably larger, owing to the organized dispensary system under which French women, in theory at least, are trained for hospital service in the War analogously to the military training of men. Two types of nurses result, the first being the Infirmière, and the second the Infirmière-Surveillante, representing an intermediary and final degree of proficiency along the lines of nursing. A diploma for the latter requires two years of service. It is stated that 12,000 women holding diplomas from the Secours aux Blessés Militaires are now at work in French hospitals, in addition to which about 10,000 women members of the society are employed in the hospitals as assistants.

A brief summary concludes the article, with emphasis on the belief that private benevolence should play no role in providing advantages which disabled men should receive as a right from their fellow-citizens. In correlating French experience with Canada's needs the author says that the Canadian Army Medical Service, already responsible for establishing the physical condition of a man on his entrance to or exit from the forces, should bear all responsibility of controlling (though not of giving) medical treatment, active or reëducational, until the recipients are discharged or granted pensions.

Nearly half of the final section of this article is in the form of appendices, referring to the various subdivisions of the subject, which contain valuable references to schools, hospitals and other institutions, together with some statistical tables and bibliography. Explanatory comments are attached in many instances to the topics considered.

THE ORGANIZATION AND AIMS OF THE ORTHOPEDIC RECONSTRUCTION HOSPITAL. This very interesting article is by Dr. Mayer, an American surgeon who was connected with the Red Cross Base Hospital Ambulance at Berlin and returned to this country upon the declaration of war. A recital of his views and experience is therefore of particular interest.

Dr. Mayer divides the injured men constituting the homeward bound cripples as follows:

1. The blind.
2. Those suffering with internal diseases; tubercular, non-tubercular, such as chronic heart and kidney diseases, et cetera.
3. The mentally deranged.
4. The group whose motor functions are impaired.

The present paper deals exclusively with the last class. On the basis of two and a half years' experience as chief surgeon to a 500-bed base hospital near Berlin he suggests the following main groups of injuries falling within this last class:

1. *The Amputated.* At the end of 1916 the number of German soldiers with leg amputations alone was 16,000. Dr. Mayer points out that after an amputation the subject is not ready for discharge from the hospital as soon as the wound is healed. The stump must be hardened by proper exercises and reduced to a constant size before an artificial limb can be fitted.

2. *Bone Injuries.* Under this he emphasizes the frequency of improperly set fractures and delayed union.

3. *Lesions in and about the Joints.* The joints may be completely obliterated by a fusion of the bones one to another or they may be stiffened by a long-continued immobilization. In the first type brilliant results apparently follow plastic operations, in which a new joint is formed by chiseling the bones apart and inserting a pad of fat or fascia.

4. *Nerve Injuries.* Rare in times of peace, these constitute a common occurrence in military surgery. The injury is usually a complete severing of the nerve and operative procedures to restore continuity form only the first step in a lengthy course of treatment, many months being required "before the fibers grow from the point of suture down to the muscle which they control."

5. *Tendon Injuries.* Dr. Mayer points out that with the present ample opportunities for studying cases much knowledge has been gained in regard to anatomical and physiological repair along these lines.

6. *Static Deformities.* He also states that, despite rigid examinations, many deformities develop in soldiers owing to the tremendous strain upon their feet, calling for the greatest care on the part of trained orthopedists. An important fact brought out by his experience is the injury which is sometimes produced by indiscriminate and unscientific massage and so-called physiotherapy. He thinks that this work should not be relegated to the hands of a masseur or physical culture teacher.

It is interesting to note that until the war there have been relatively few advances in connection with artificial limbs, the trade having been handed down from one "master" to another, with little or no change. In Germany the Society of Engineers offered a prize for the best artificial hand and arm, as a result of which some unique types were discovered, such as the artificial hand invented by an untrained peasant, August Keller. In the opinion of Dr. Mayer this is unquestionably the best form of prosthesis for the farmer. Dr. Mayer thinks that the possibilities of development in this connection by the Yankee mind are very great.

In concluding the article the author indicates the importance of properly selecting the personnel for hospitals engaged in such work. With the selection of the chief orthopedic surgeons rests success or failure. He must be a master of his art and must also possess a social conscience for the individual needs of his patients. Appended is a table giving the list of personnel for a 500-bed hospital. Dr. Mayer emphasizes what has been so repeatedly brought out, that neither private charity nor haphazard local organizations must be allowed to take care of these men. The responsibility for their care must rest upon the State.

The Red Cross Institute for Crippled Soldiers and Sailors. Mr. Devine outlines the program of the Red Cross Institute for Crippled Soldiers and Sailors, inaugurated by a contribution of $50,000 from Mr. Jeremiah Milbank, of New York City, who also put at the disposal of the Red Cross the building at 23d Street and 4th Avenue, originally occupied by the College of Physicians and Surgeons. It is understood that the institute will begin its activities where the surgeons and orthopedists cease theirs, and will concern itself with the question of vocational reëducation. A preliminary investigation is being made to cover the work accomplished to date elsewhere, and includes visits to France, England and Canada. Any definite outline of the plans of the institute at the present time would be premature, but it is clear to Mr. Devine that the program must include a study of the needs and abilities of the individual man by medical, educational and social experts There must be opportunities for learning a great variety of occupations and methods for placing men when they are qualified to accept positions. It is evident that the development of this institute will be along ambitious lines, which will doubtless be followed with the greatest interest.

Vocational Schools for War Cripples in France. Under this title is presented an interesting summary of the activities of various schools for this work, including those at Paris, Bourges, Bordeaux and elsewhere: Current Notes on the Organization of After-care for War Cripples in Germany and War Cripples at the Agricultural Training Station, Gross-Tarpen, near Graudenz, Germany.

Two short articles of interest are those bearing upon the care of war cripples in Germany. Nothing particularly new is advanced, but the text is of interest because representing conditions in Germany of which we ordinarily hear little. It is at least developed in these articles that provisions existing on paper for the care of such dependents are not necessarily equally developed in actuality.

To quote the article:

"Practically every village in, say, the Province of Brandenburg flourishes a shingle with a red eagle and the inscription 'Kriegsbeschädigtenfursorgestelle' (war cripples' welfare bureau), but in most cases the posting of the decorative placard is as far as the work of the welfare bureau goes. Things are no better in most of the other provinces.

"The Reichsausschuss für Kriegsbeschädigtenfursorge (federal committee for war cripples' welfare work) has provided for the task in question a great working program on thoroughly commendable basic principles. All of these presuppose the coöperation of an extensive circle of agencies. But the mass of the people, and most particularly the war cripples themselves, can place their confidence in this organization only if all the industries work together, and more particularly the labor interests are adequately represented.

"As a rule, individual war cripples, upon discharge from military welfare agencies, come into contact with the local business offices only, usually the civil war cripples' welfare bureaus. The chief purposes of the latter are vocational guidance and placement in a suitable and remunerative position. The latter task is at present comparatively easy, since work can now be provided for men who retain only half their working capacity—or even less. But things will be different after the war, when, upon the return current of healthy workers with full working powers, war cripples will have to compete with sound men in the daily struggle for existence. Then the lack of a centralized welfare organization will become a calamity with most serious consequences."

R. P.

The Technic of the Carrel-Dakin Treatment.—McCartney and Mewburn (*British Med. Jour.*, February 9, 1918) describe especially those details which have been introduced into the procedure during their year's experience with it. The solution is prepared daily in the dispensary according to the method of Dr. Daufresne as set forth in the circular of the laboratories of the Rockefeller Institute at Compiègne, issued December 15, 1917. The potassium permanganate is added after the solution reaches the ward, and the amount is 5 mg. to each liter of Dakin's solution. The strength of the hypochlorite should not be over 0.485 per cent., as stronger solutions often cause the wounds to develop a scalded, white appearance. A series of tests was made to see the action of light on the solutions. It was found that if the bottles containing the fluid are kept covered with bags of heavy duck impregnated with a brown floor stain the solution will retain its potency for forty-eight hours. The disinfection of the Carrel tubes and the preparation of the vaselin pads are most important. The Carrel tubes after use are syringed out with warm water, scrubbed with a brush, soaked all night in Dakin's solution, washed off with ether and then boiled for

thirty minutes in a caustic soda solution. In the vaselin pads, cheesecloth, with twenty-four threads to the inch, gives best results. When the method, which is given in detail, is followed the resulting pads are thoroughly impregnated and adhere perfectly to the skin, allowing no Dakin solution to overflow on to the skin. The medical officer invariably should do all the dressings, as in no other way can there be certainty of the technic. It is possible for one medical officer to dress 50 cases a day if other duties are light. As assistants are one nursing sister and two orderlies, one of whom may be an intelligent convalescent patient. Both nurse and head orderly should be fixtures in the ward, as satisfactory team work and thorough asepsis are only obtained by permanent assistants. The duties of each are carefully planned and carried out. The essential point of the dressing technic is that the wounds, tubes and dressings are on no account touched by the hands. Everything is handled solely by clean dressing forceps. The various stages of the dressings are detailed in order. By these methods there have been obtained in the majority of cases most satisfactory and even surprising results. W. H. F. A.

Dermatology in Connection with the War.—Macleod (*Practitioner*, February, 1918) first discusses dermatitis due to the handling of high explosives, such as tetryl, trinitrotoluene and lyddite. The dermatitis produced by these different explosives is practidally indistinguishable, though the staining of the skin associated with each may be characteristic; also the explosives differ to a considerable extent in their capacity for being absorbed and for giving rise to toxic symptoms. The irritating properties of tetryl are so great that it is liable to produce dermatitis in a considerable proportion of those working with it. In its powdery form it is most potent as an irritant. In the process of sieving the powder is given off in a cloud, which becomes deposited on the floors, tables, clothes and exposed parts of the skin. It causes a yellow or apricot-staining of the skin and hair, and this is more liable to occur in skins moist with perspiration than in those which are naturally dry. The dermatitis usually comes out within a fortnight after beginning work with the substance. It varies from simple erythema to definite edema or deep-seated vesication, and is associated with itching so distressing as to interfere with sleep. Only exposed parts are usually involved. Eyelids are apt to be severely affected, and may be so swollen, as almost to close the eyes, and there is some accompanying conjunctivitis. Once an attack has occurred the skin becomes so abnormally sensitive that even if the worker is transferred to another department a recurrence may be caused simply by contact with clothes or even with paper soiled with the tetryl. Cases have been met with not only in the workers themselves but even in those living with them, from handling or washing soiled clothes which have been worn in the factory. Symptoms of absorption are, as a rule, absent or transitory. There may be effects from inhalation and swallowing resulting from irritation of mucous membranes of the upper respiratory passages and of the stomach. The dermatitis heals rapidly under simple local treatment when the worker is removed from exposure to the irritant, but lead lotions must not be used. As preventive measures, in addition to cool clean workrooms, close-fitting clothing, thorough washing of skin after exposure,

the hands may be hardened with methylated spirits and the face protected with a powder of zinc oxide and starch. Trinitrotoluene is a highly irritating substance, given off in the form of a fine dust in sieving or filling canisters and shells, which settles on the operators and insinuates itself beneath the clothing. On the skin it gives rise to a severe form of dermatitis, and by being absorbed may lead to serious and sometimes fatal toxic symptoms. The superficial yellowish staining is especially noticeable in the creases of the palms, but is not so intense as that caused by tetryl. In severe cases of dermatitis, in addition to edema, there is a papulovesicular or bulbous eruption, which on healing is followed by coarse exfoliation. The vesicles and bullæ are apt to become secondarily infected. There is always more or less intense itching. The general effects which may be of a serious character consist of toxic gastritis, toxic jaundice and rarely toxic anemia. In toxic gastritis the high-colored urine contains trinitrotoluene. Some individuals appear immune while others may show the dermatitis within a week after contact with the substance. It is most common in hot weather, and is specially liable to occur if the skin is greasy, for the trinitrotoluene is soluble in oil. As a prelude to treatment all traces must be removed by gently rubbing the skin or hair with ether or oil. Preventive measures are similar to those used in connection with tetryl. Lyddite has an irritating action due to the picric acid it contains, and causes a dermatitis similar to that caused by trinitrotoluene. It gives a canary yellow or greenish staining of the skin. A number of cases of dermatitis has been reported from handling powder from high-explosive bombs dropped in air raids. The writer also relates his experience with the open method of healing burns in hospitals of the Royal Flying Corps. Since the outbreak of the war the treatment of burns has attracted increased attention due to the frequency of burns received in the field from liquid fire and petrol and in connection with aëroplane crashes. The open method in which healing is allowed to take place under a natural scab the writer considers it in some ways preferable to the paraffin treatment. It is particularly useful in burns of the leg and face, especially in the healing of the granulating surfaces after the separation of the eschar. The raw surface is powdered over with a bland aseptic powder. This contains sterilized stearate of zinc or magnesium carbonate, and a sample formula is given. The powder is added from time to time until the scab becomes a coarse, yellowish-green crust, a quarter or half-inch in thickness. In many cases this can be left alone until the wound heals. But should the discharge beneath become excessive it may be necessary to remove a small portion and bathe away the seropurulent fluid and reapply the powder. The method is useful as not necessitating periodical redressings, and leads to the formation of a pliant scar, which has comparatively little tendency to contract. W. H. F. A.

The Nutritive Value of Straw Treated with Alkali in the Dietary of Man.—RUBNER (*Arch. f. Physiol.*, 1917, p. 339) states that straw treated with alkali and then used as a diluent for bread when given to man increases the nitrogen and energy loss in the feces to a greater extent than it could furnish either to him. G. L.

REVIEWS

PROGRESSIVE MEDICINE. A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. Vol. IV, December, 1917, and Vol. I, March, 1918. Philadelphia and New York: Lea & Febiger.

THE last volume of *Progressive Medicine* for 1917 appeared in December. The first 115 pages is given up to an exhaustive review of the most recent advances in diseases of the digestive tract and allied organs, the liver, the pancreas and the peritoneum. Dr. M. E. Rehfuss discusses in this article the recent literature on the above subjects, including diseases of the tongue and mouth and of the esophagus and stomach, to the latter of which he devotes by far the greater part of his contribution. His discussion is full and interesting and should be useful to the general practitioner. Dr. J. Harold Austin then follows with a discussion of the literature on diseases of the kidney. This review deals with renal physiology, experimental nephritis, the renal functional tests, uremia and acidosis, and the remainder of the article is devoted to nephritis, including trench nephritis, ureteral obstruction and the renal function in pregnancy. He concludes his contribution with an article on the diagnosis of renal tuberculosis. Dr. Charles W. Bonney then discusses genito-urinary diseases, including the surgical conditions of the kidneys, diseases of the bladder, the penis and urethra, and then follows a review of the literature on military surgery by Dr. Joseph C. Bloodgood.

Those who are familiar with the admirable review on surgery that Dr. Bloodgood has contributed for many years to *Progressive Medicine* will welcome the critical review on military surgery that this author has written for the December number of this journal. At a time when so many of the medical profession of this country have entered or are about to enter the military service it is of vital importance that they should thoroughly understand the great problems that are confronting the Medical Department of the Army.

He begins by calling attention to some of the most useful new books on military medicine and surgery, and then points out the wonderful opportunities for special training and education that the Surgeon-General of the Army has so wisely provided for medical officers.

Shock is an important factor in the ultimate prognosis of the wounded, and Dr. Bloodgood deals with this subject at considerable length. He cites the opinions of those who have had the best opportunity to observe the condition of shock as it occurs in and near the trenches; discusses the role played by cold, fatigue, painful dressings and rough transportation in its production and gives valuable suggestions for combating it.

After touching on shell-shock, he digresses and takes up in detail first aid as applied to industries, a subject of greatest economic importance in peace as well as in war, and one in which he has always taken an ardent interest.

Much uncertainty exists in the minds of many as to the exact disposition and duties of the various units of the medical department in combat. This entire subject is well handled, with unusual clearness, by the reviewer. As the basis of his discussion he avails himself of the several articles and notes that have recently been contributed by Colonel Goodwin, of the British Royal Army Medical Corps along this line. In his review, Dr. Bloodgood notes the steps necessary for the transportation of the wounded from the firing line back to the base hospitals. He also takes up in detail the organization, equipment and duties of the different medical units operating in the zone of the advance as well as those on the line of communication and at the base. The comparison which he draws between the disposition of the British medical personnel in the theater of operations and that employed by our own army is most helpful and instructive. He also comments at length on many valuable statements and suggestions that Colonel Goodwin has made from time to time on shock, wound treatment, gas gangrene, fractures and their treatment at the front, abdominal wounds, trench-foot and gas-poisoning. He also reviews the question of first aid in war, especially in the trenches, and the first-aid packages of the English and American armies. This involves a discussion of the mooted question of the use of iodin by the soldiers themselves. The weight of evidence is against its routine use by the unskilled.

The most striking feature of Dr. Bloodgood's contribution is his plea for the universal adoption of the Carrel-Dakin treatment of infected wounds. He describes the wonderful hospital for the treatment of wounds by the Carrel-Dakin method that has been established by the Rockefeller Institute, where, under the guidance of Carrel himself, Medical Reserve Officers are instructed in all the details of the method.

No less important is Dr. Bloodgood's account of military ortho-

pedics in its broadest sense. No one has done more to develop this branch of surgery than Colonel Robert Jones, of Liverpool.

There is no part of Dr. Bloodgood's article more generally useful to officers of the Medical Reserve Corps than that which deals with the soldier's feet, and more particularly with flat-foot, its diagnosis, significance and management. Like most writers on this subject he is lavish in his praise and approval of the United States Army shoe devised by Colonel Weimer.

Under Surgical Bacteriology Dr. Bloodgood expresses the hope that the antitoxin for the gas-bacillus infection discovered by Carroll G. Bull will prove as efficacious in combating this dread infection in human cases as it has in animal experimentation.

In conclusion he outlines the extensive plans that are being made for the reconstruction and reëducation of the large number of wounded that must inevitably result from this war.

It would be difficult to find a more complete, concise review of the essentials of modern military surgery than is embodied in Dr. Bloodgood's article? It has the added advantage of being replete with illuminating comments based upon the extensive surgical experience of the author. The medical officers, and particularly the Medical Reserve Officers, who fail to avail themselves of this contribution by Dr. Bloodgood, seriously neglect a timely and valuable educational opportunity.

The concluding 97 pages of this volume contain a discussion of the newest achievements in practical therapeutics by Dr. H. R. M. Landis, who takes up at considerable length the latest advances in this line, and in his usual interesting and enlightening way brings to our notice the literature on adrenalin, alcohol, ammonium chloride, asperin, camphor, etc.

Vol. I, 1918, opens with an article of 92 pages by Dr. C. H. Frazier on surgery of the head, neck and breast, and deals largely with war surgery of these parts. He discusses the literature on gunshot injuries extensively, and concludes with surgery of the mammary gland. Dr. George P. Müller then follows with a review of the surgery of the thorax, including diseases of the breast, and the larger part of his article also deals with war surgery. Dr. John Ruhräh then discusses in his usual interesting and exhaustive way the literature on infectious diseases and gives an abstract of what the Rockefeller Foundation has done with war relief work in China with hookworm disease and the Yellow Fever Commission in South America. He calls attention to the value of flavine and brilliant green as antiseptics and to the keeping qualities of therapeutic serums. He then takes up the subject of dysentery carriers, bronchial asthma, cerebrospinal fever, the skin reactions in infectious diarrhea, Hodgkin's disease, hookworm disease, epidemic nephritis, and devotes 27 pages to the subject of poliomyelitis. He discusses trench fever and trench-foot, typhoid and typhus fever, Weil's

disease, and concludes with an article on whooping cough. Dr. Floyd M. Crandall refers to the advances in diseases of children, particularly the effect of civilization upon children's diseases. He then in turn discusses the diathesis in childhood, acidosis in children, luetic nephritis in infancy and childhood, the influence of vitamins, stenosis of the pylorus, chorea, chronic intestinal indigestion in children, and concludes his article with ten pages on infant-feeding. including a table of food allowances for children under two years up to seventeen years. The volume concludes with an article of 82 pages by Dr. George M. Coates, who devotes this space to the more recent advances in rhinology, laryngology and otology, giving particular attention to the military phases of these subjects. The volume, though not as large as usual, is complete, and should prove both interesting and useful to all medical and surgical men.

S. S.

A Pocket Formulary. By E. Quin Thornton, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College, Philadelphia. Eleventh edition. Pp. 292. Philadelphia: Lea & Febiger, 1918.

That there is a broad and legitimate field of usefulness for works of this character is self-evident, though it is not at all meant to replace individual thought on the part of the practitioner. Even the best informed physicians may at times overlook an appropriate drug or combinations that make for palatability and pharmaceutical elegance.

This *Formulary* serves its purpose well, and in revising the author has enhanced its value by signifying the indications as to the use of each formula.

C. N. S.

Human Physiology. By Professor Luigi Lucaiani, Director of the Royal University of Rome. Translated by Frances A. Welby. Vol. IV, The Sense Organs. Pp. 519; 217 illustrations. London: Macmillan & Co.

This volume deals with the physiology of the sense organs, and contains chapters on cutaneous sensibility, sensibility of the internal organs, taste, smell and hearing. Three chapters are devoted to the visual apparatus under the headings Dioptric Mechanism of the Eye, Retinal Excitation and Visual Stimulation and Ocular Movements and Visual Perceptions. The final chapter deals with the psychophysical phenomena of consciousness and sleep. In each of these subjects numerous researches are discussed and the points of view and results of the investigators are reviewed in detail, while here and there the author gives his own opinion to illumine the path

of the reader. A book written on this plan excels not in giving general results but in showing, by tracing the growth of our knowledge, how present-day conceptions have been reached. This historical analysis is at once the most interesting and the most elusive side of the study of a science. To use this form of presentation necessitates many detailed descriptions, but it is the distinctive achievement of this book that it is eminently readable in spite of the minute details often entered into. Considering the experience and reputation of the author and his long scientific career, one may regard the views assembled here as those most tenable in the light of present knowledge and of lasting value, because necessary for consideration in any further progress of the science. W. H. F. A.

LORD LISTER. By SIR RICKMAN JOHN GODLEE, BT. Pp. 676; 33 illustrations. London and New York: Macmillan & Co.

IN these days of warfare and military surgery, when the treatment of infected wounds and the study of new antiseptics become of supreme importance, one is brought back vividly by this book to Lister's early day, when he began to deal with the ever-present foul wounds in civil hospital practice. Problems similar to those which he sought to solve present themselves under a somewhat different form, and after the interval of years, in which the modified form of antisepsis known as asepsis has been to the fore, we find the search for methods of antisepsis demanding increased attention.

This life of Lister, interesting as the record of a personality, is still more important as a contribution to our knowledge of the working out of a great idea. The author, a nephew of Lister, lived for many years in close personal contact with him, associating with him, both in the hospital wards and in the laboratory, so that he was well fitted for the task of biographer. In keeping with Lister's expressed desire it is chiefly a record of what he accomplished for science and for surgery, but we are also shown many glimpses of his daily life without which such a record would be incomplete. After reading of Lister's scientific activities, one may safely conclude that he would have made his mark in whichever branch of science he might have chosen to follow. Throughout his life he combined creative laboratory work with the practical problems which he sought to solve. Acquainted with microscopy from his earliest years, when his father was engaged in making great improvements in the lenses of the microscope, he used this instrument successively in normal histological, physiological, pathological and bacteriological studies, and in all of them he contributed something of value. Perhaps the most interesting part of the book is that dealing with the events leading up to his first successful treatment of a case by

the antiseptic method, using carbolic acid. This was in 1866, and this represents the beginning of his search for and study of new antiseptics, which continued practically to the end of his life. To everyone interested in the progress of medicine this volume will be of lasting value, constituting, as it does, the record of a great man who accomplished great results. W. H. F. A.

A Text-book of Obstetrics. By Barton Cooke Hirst, M.D., Professor of Obstetrics in the University of Pennsylvania. Eighth edition, revised. Pp. 863; 715 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

In bringing forth the eighth edition of this valuable practical book the author has revised the text so that the subject matter has been brought up to date and due attention has been given to all of the worthy additions to the art of obstetrics that have been presented to the profession since the last revision of the book six years ago. There is little that a reviewer can say about a book of this kind that has long since become a favorite in the average medical library. While it is hardly so complete and exhaustive as one or two other text-books on the subject that have been presented in recent years, it is pleasing to note that the author is continually revising it, so that the book can always stand on its own merits rather than being obliged to depend on its early editions for its prestige. The literary style of the author, together with the many amusing anecdotes that are used by way of illustration, serve to make the text very pleasant reading, and one that should specially appeal to the medical student. F. B. B.

The Technic of the Irrigation Treatment of Wounds by the Carrel Method. By J. Dumas and Anne Carrel. Translated by Adrian V. S. Lambert, M.D., Acting Professor of Surgery in the Columbian University. Pp. 81; 11 illustrations. New York: Paul B. Hoeber, 1917.

This small book was written by Madame Carrel primarily for nurses, in order that they might have a clear, short account of the various details of the technic and an accurate description of the apparatus used in carrying it out. An appreciative introduction is furnished by the noted and still active American surgeon W. W. Keen. Those wishing to become proficient in the employment of this method of treatment will find this book devoid of confusing theoretical considerations. The stage of discussion concerning the value and importance of this new way of handling infected wounds having passed we are prepared to welcome such a brief, complete and authoritative treatise on the subject. T. T. T.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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Volkmann's Ischemic Paralysis and Contracture.—TAYLOR (*Ann. Surg.*, 1917, lxv, 28) says that experimental work and clinical observation point to traumatic myostitis as the fundamental condition in causing Volkmann's ischemic contracture. The pressure causing the muscle disorganization is both internal and external: internal because the flexor muscles are firmly confined by their envelope of aponeurosis and bone, and external because of tight dressings or the position of acute flexion of the elbow. The degenerated muscle substance is replaced by connective tissue, the contraction of which causes the typical deformity. The damage to the muscle may be very slight, it may be complete, or it may be of any grade between these two extremes, and it is impossible clinically at an early time to determine just how extensive the damage is. Pressure sloughs and abscesses are common on the ulnar side of the wrist and on the flexor prominence just below the elbow. When present these abscesses usually burrow to the deeper structures, heal very slowly and add greatly to the cicatricial rigidity. Nerve injury is purely a complication. It occurs in about 60 per cent. of the cases. It may be primary as the result of the accident, or secondary as the result of the pressure of the swollen muscles, or occur, more frequently, later as the result of cicatricial constriction. The ulnar and median nerves are most often involved and are usually constricted a short distance below the elbow. The prognosis should, as a rule, be unfavorable. Inasmuch as it is impossible to determine clinically the exact amount of damage, an accurate prognosis can not be given until the reaction to proper treatment has been watched for a time. In children from one to fourteen years of age, in injuries about the elbow region, tight dressings should be avoided, as well as extreme flexion of the elbow. All cases should be watched for undue pain, swelling and cyanosis, so that prompt measures may be taken, if necessary, to prevent the full development of the lesion. If in spite of these measures

the swelling and cyanosis increase, one should attempt decompression of the flexor muscles by splitting the deep aponeurosis longitudinally, either subcutaneously or together with the skin if that is edematous and shiny. Late operation is done either to lengthen all the tendons of the contracted muscles to permit simultaneous extension of the fingers, hand and wrist to a straight line, or to shorten the bones sufficiently to attain the same result. After an operation has mechanically relieved the deformity, the real work of rehabilitation must be done by a prolonged course of physical therapeutics. Therefore it would seem preferable to avoid the trouble and risk of operation by employing the method of mechanical overstretching of the contractured tissues. This method combined with physical therapeutics obtains results which for promptness and quality are as good or better than those obtained by operation. This may be accomplished by the Jones method of rigid splints or by the method preferred by the author, which may be called the elastic traction method. Persistence in treatment is the only hope of success in the severe cases.

Enterostomy for Ileus.—Doud (*Ann. Surg.*, 1917, lxv, 95) says that the operation of enterostomy is a very old one, at least one hundred and twenty-nine years. It is resorted to now much more frequently than it used to be. The details of the procedure differ with the case. Sometimes, without anesthesia, a little opening is made in a loop of the intestine which presents in the drainage wound; sometimes under local anesthesia, a small abdominal incision, a catheter or small tube, is tied or stitched into an opening in the intestine, and a few Lambert stitches secure the intestine to the abdominal wall; sometimes, under general anesthesia, a search is made for a definite obstruction, and failing to find this, an enterostomy opening is made with careful provision for the subsequent closure of the wound. Sometimes at the termination of a primary operation in unfavorable cases, an enterostomy is done as a safeguard. In all cases the stoma should be as small as will be efficient. Nothing in surgery is more dramatic than the improvement which comes from a fortunate enterostomy. A patient who is almost moribund before the operation is, a few hours later, comfortable, bright, and hungry. The obstruction is frequently temporary. If there are many angulations in a moderately inflamed intestine, the total obstruction may be sufficient to produce stasis. Such obstruction, however, ceases if the distention can be relieved, and if the inflammation subsides. In closing the opening later, Doud loosens the intestine from its adhesions to the abdominal wall, but a very wide exposure of the peritoneum is avoided. Through-and-through stitches invert the edges of the intestinal stoma. Lembert stitches reinforce the suture line, and almost complete closure of the abdominal wall, in layers, has followed. This closure has not been absolutely complete, as provision has always been made for drainage at a little distance from the intestinal sutures. Intestinal resection is a severe operation and is to be avoided when possible.

Fatal Complications of Percy's "Cold Iron" Method in the Treatment of Inoperable Carcinoma of the Cervix. — Leonard and Dayton (*Surg., Gynec., and Obst.*, 1917, xxiv, 156) says the

Percy method consists in the application of long-continued low heat in the treatment of otherwise inoperable carcinoma of the uterus. This procedure is based upon a principle claimed by Percy, namely, that carcinoma cells are killed by low penetrating heat insufficient to destroy normal tissues. The Percy method has been widely adopted and the results so far reported have been almost uniformly favorable. He summarizes his observations and full reports of two fatal cases treated in the Gynecological Clinic of the Johns Hopkins Hospital. The primary effect of the Percy cautery is to cause a necrotic mass extending more or less uniformly in all directions from the coagulating point. A mass of sloughing coagulated tissue of this type offers an ideal medium for the growth of microörganisms. It will probably be found impossible to prevent infection of this area, and once infected the thrombosed vessels of the region may offer a ready entrance into the system. Therefore the danger of a septicemia is considerable. The authors are convinced, from their short experience with Dr. Percy's method, that fatalities must have been frequent wherever this method has been employed extensively, yet they were able to find only one complete report of a fatal case in the literature, that of Dr. Boldt. They conclude that the prolonged treatment of large carcinomatous masses by low heat may result in a rapidly fatal outcome with lesions similar to those in cases of fatal cutaneous burns. The necrotic mass produced by the cautery forms a particularly favorable medium for bacterial growth. The organisms may spread to the surrounding tissues or reach the general circulation through the local thrombosed vessels. It seems probable that the greatest danger in the application of the Percy cautery is a local infection and a subsequent general sepsis. Finally, the technic is ineffectual in eradicating the carcinoma. There is no evidence from these two cases that carcinoma is more susceptible to heat than is normal tissue.

Observations on Gas-bacillus Infection in France.—JUDD (*Surg., Gynec. and Obst.*, 1917, xxv, 113) says that of all the classes of wounded seen in the present European war the most terrible and formidable are those of the so-called gas-bacillus infection. Modern trench warfare with the accompanying difficulties in providing cleanliness exposes a large proportion of wounded to the dangers of gas-bacillus infection. The majority of cases follow shell wounds when a piece of contaminated clothing is carried into the depths of the wound by the projectile. Among the varieties of microörganisms present in the wounds, the bacilli perfringens are generally accepted as the causative organisms. These bacilli appear in the wound from the ninth to the twelfth hour. The aërobic bacteria appear about the forty-eighth hour. The symptoms of the infection appear early, usually on the second day. The parts of the body most often affected are the legs on account of the likelihood of their becoming contaminated by dirt and fecal matter. It is of vital importance that the diagnosis be made early. Pain, swelling and tension of the wound with rapidity of the pulse are important early symptoms. Vesicles, discoloration of the skin, gas formation and odor should be considered later symptoms. The prognosis depends on whether the patient receives proper early treatment. Trench hygiene and personal cleanliness are vital prophylactic measures.

Early incision of the wound with removal of the foreign bodies, cleansing of the wound and excision of damaged tissue doomed to slough are the correct surgical procedure of prevention. When the infection is once established, well placed, deep incisions exposing the deeper tissues to the air, are indispensable. For the clinical treatment of the wound, Dakin's solution has given the best results. Amputation must be resorted to in many cases and should not be delayed beyond the proper period.

Intrapericardial Traumatic Hemorrhage.—Rhodes (*Ann. Surg.*, lxvi, 1917, 44) says that in general very few traumatic lesions of the thorax demand operative relief. But there is a definite type of thoracic injury in which interference must be prompt, and no considerations such as the critical condition of the patient must interfere with such operative attack. This refers to acute hemorrhage of large amount into the pericardial sac, accompanied by very slight opportunity for the free outlet of the hemorrhage. Rhodes operated on 2 cases. The first was a stab wound of the pericardium with intrapericardial hemorrhage. A rectangular osteoplastic flap was made in the following manner: An incision was made over the middle of the sternum, extending from the second to the fifth costal cartilages. From the upper and lower ends of this, incisions were made at right angles to it for a distance of five inches. This skin and muscle flap was dissected back and the cartilages of the third and fifth ribs were divided subperichondrically. The fourth was already divided by the injury. The intercostal spaces were then divided and the whole osteoplastic flap bent backward, breaking the ribs, probably at the junction of the cartilage and rib. The internal mammary artery was ligated. This gave splendid access to the anterior mediastinum. The triangularis sterni was incised and pushed aside, the pleura was seen to lie very close to the left sternal margin, and the rent was seen where the knife had penetrated. When the pericardium was opened a tremendous gush of blood came out, apparently under tension. No stab wound of the heart was found, the source of the hemorrhage being found to be a large pericardial vessel. This was ligated and the field remained dry. The wound was closed without drainage, the pericardial sac being previously washed out with salt solution. He left the hospital nineteen days after admission with a perfect cosmetic result. Heart and lung action was normal. The second case was one of stab wound of the pericardium and right ventricle intrapericardial hemorrhage; and unsuccessful attempt at heart suture. He concludes that in practically all cases of stab wound of the heart an accompanying injury of the pleura occurs, usually, resulting in a pneumothorax. Extreme symptoms of respiratory embarrassment should be considered as caused by the heart tamponade, and not by the pneumothorax alone. The tamponade must be relieved at once. These cases stand ether anesthesia well. The incision used in these cases gives splendid access to the heart and gives perfect functional and cosmetic results. Drainage is not necessary, but the sac should be washed out before closing, preferably with salt solution.

THERAPEUTICS

UNDER THE CHARGE OF

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The Pharmacology of the Oil of Chenopodium.—SALANT'S (*Jour. Am. Med. Assn.*, 1917, lxix, 2016) experiments on animals (rabbits, cats, etc.), indicate that oil of chenopodium, even in very small quantities, may prove very toxic. He notes that sensitiveness to the oil persists for from five to nine days and warns that the repetition of a non-effective dose within this period may cause serious symptoms or even death. The toxicity of oil of chenopodium varies largely with the nutritional condition of the animal. Fasting or poorly nourished animals succumbed to much smaller doses than did those that had been receiving a carbohydrate-rich diet for sever aldays before the oil was given, or when the administration of oil of chenopodium was preceded by a sufficient quantity of a fatty oil, such as, olive, cocoanut, or castor oil. As regards its therapeutic use, Salant concludes that oil of chenopodium should be used with caution for internal medication as it has a tendency to affect the central nervous system, the heart, respiration, the digestive organs, and the kidneys. In renal or cardiac disorders the oil should be given in small doses only, while in advanced chronic nephritis or heart disease its use would seem to be altogether contraindicated. As the liver undoubtedly plays an important part in detoxifying oil of chenopodium, while changes in the gastric and intestinal mucosa may accelerate its absorption into the circulation, it may prove more toxic in hepatic and gastro-intestinal diseases. A diet containing a liberal amount of fats and carbohydrates, fed for at least several days before the treatment is instituted, may render the drug much safer. The routine administration of large doses of castor oil before and after the oil of chenopodium may be of prophylactic value. In the treatment of poisoning, Salant recommends gastric lavage since absorption of the oil from the stomach is slow; as, however, absorption from the duodenum is rapid, lavage must not be too long delayed. No chemical antidote to oil of chenopodium has been found; the treatment, therefore, must be symptomatic. Experiments on the isolated heart show that digitalis and epinephrin are excellent antagonists; caffein, on the contrary, appears to increase the toxic action of the oil.

Tartar Emetic in the Treatment of Malaria.—FALCONER and ANDERSON (*Lancet*, 1917, cxciii, 743) treated 8 cases of malaria by the intravenous injection of tartar emetic as suggested by Rogers. Of the 8 cases, 2 were mixed infections, 1 subtertian malaria, and 5 benign tertian malaria, 3 of which showed gametocytes. In the two mixed infections the crescents disappeared in both, the benign tertian parasites persisting in one and disappearing in the other. In the subtertian crescent infection the crescents disappeared after four injections of

tartar emetic. Despite their disappearance the patient had three typical clinical attacks of malaria though the parasites could not again be demonstrated in the peripheral blood. In none of the five benign tertian infections did the parasites disappear from the blood stream until large doses of quinin had been administered. In 2 of the 3 cases where gametocytes were originally seen this type of organism was found subsequent to the tartar emetic treatment. Neither in the subtertian nor in benign tertian cases was any marked clinical improvement noted, and in the benign case the tartar emetic did not appear to exert the slightest effect on the parasite. The results of treatment were so disappointing that the authors do not feel justified in continuing their observations.

Cerebrospinal Fever: The Mode of Infection of the Meninges.—Worster-Drought and Kennedy (*Lancet*, 1917, cxciii, 711) admit that the nasopharynx is the primary portal of entry of the meningococcus in cases of cerebrospinal fever. From their clinical and bacteriological study of cerebrospinal meningitis they conclude that the meninges are rarely involved by direct extension from the nasopharynx *via* the middle ear, sphenoidal or ethmoidal sinuses. The usual mode of meningeal involvement is by way of the blood stream. In the ordinary type of cases the coccus is carried to the meninges by the blood within a few hours (usually less than forty-eight) without definitely infecting the blood itself. In these cases the blood stream is purely a carrier, and there is little or no proliferation of the cocci during their transit. In severe cases, however, true blood infection (septicemia) occurs. In the fulminating cases septicemia overshadows the meningitis and at autopsy the meninges show no typical signs of inflammation. In rare cases the organism may remain infecting the blood alone for a considerable time before finally reaching the meninges; or the patient may die of septicemia without showing any signs of meningitis. In other cases the meningococcus invading the blood may also invade structures other than the meninges. In 1 case of meningococcal septicemia the aortic valve showed ulcerative endocarditis and perforation of one cusp. Cocci were demonstrable in the vegetations. The brain was pale and anemic. There was no meningitis. From an analysis of the other cases the authors conclude that catarrhal conditions predispose to meningococcal infection, but the meningococcus does not necessarily produce nasopharyngeal catarrh.

The Red Blood Cell Count and Hemoglobin Content of the Blood in Disordered Action of the Heart.—Levy (*British Med. Jour.*, 1917, ii, 715) reports the results of a most careful examination of 15 patients at Hampstead Military Hospital. They were unselected cases of disordered action of the heart of all degrees of severity. None of these patients had been "gassed" and none exhibited unusual symptoms, such as nocturnal dyspnea. The average red blood cell count of the 15 patients was 5,008,007. Range: 4,892,000 to 6,600,000. This is quite in excess of anything previously reported in healthy individuals, and is the more remarkable in view of the fact that these men were all invalids who had spent a considerable time in the hospital before the estimation was made. One-third of these patients had a count of over 6,000,000 and 53 per cent. had a count of 5,900,000 or more. The

hemoglobin content was for the most part below the normal 100 per cent., the average being 93.4 per cent. Range: 87 to 100 per cent. The average color index was 0.8. Range: 0.74 to 0.9. No relation exists between the red blood count and the severity of the cardiac disorder. Levy is unable to suggest the significance of this polyerythrocythemic condition.

A Note on Serum Sickness in Cerebrospinal Meningitis.—KERR (*Lancet*, 1917, cxciii, 822) was led to the present study by the fact that of a series of 48 cases of cerebrospinal fever treated with Flexner's serum no less than 76 per cent. suffered from serum sickness. The reactions were, as a rule, quite sharp and in most cases were accompanied by considerable fever. The outstanding feature was, as usual, the rash, which often started as an urticaria and then ran into a multiform erythema. Very severe arthritis was noted in 6 cases; adenitis in 2; in 9 patients a prodromal fever occurred from twelve to twenty-four hours before the appearance of the rash and was accompand by an exascerbation or relapse of the meningeal signs. More than two-thirds of the reactions commenced on the eighth, ninth, or tenth days after the first injection; the symptoms usually lasted several days. The author points out that the introduction of horse serum into the spinal canal is liable to set up a local reaction which may be described as an aseptic meningitis. A previously clear fluid may become turbid and a slightly turbid fluid may become more opaque. These changes are due to the presence of an increased number of polymorphonuclear leukocytes. When a spinal fluid is so changed the serum reaction and the rash usually follow within a few days, and it appears that a meningeal reaction is a prodromal sign of the more usual phenomena. Kerr finds that Fehling's solution is reduced by all the fluids that become more turbid as the result of a serum reaction. The large number of rashes in this series of cases suggests that the intrathecal injection is more liable to cause them than the subcutaneous. Kerr does not believe that the method of administration is at fault. He ascribes the large number of reactions to some peculiarity of the horses from which the serum is obtained. The occurrence of the rash is not much influenced by the dosage. Kerr believes that many cerebrospinal patients are much improved by these injections and that they are no cause for anxiety. He suggests that the benefit may be due to some stimulus of metabolism or of the processes of repair. He is convinced that in cases which are apparently threatening to enter the chronic stage the improvement which follows serum sickness may be ascribed to the almost perfect counter-irritation offered by the widespread pruritic rash. Kerr does not inject serum in the presence of a serum reaction unless the diplococci in the spinal fluid appear to be increasing. The Fehling test is a useful means of determining whether a rise in temperature with an exacerbation of meningeal symptoms is caused by a serum reaction or by a recrudescence of the disease.

Serum Disease after Intrathecal Injections of Serum.—In this paper ROLLESTON (*Lancet*, 1917, cxciii, 821) compares the manifestations of serum sickness after the intrathecal and after the hypodermic method of serum injection. His conclusions are based on the clinical

notes of 96 cases of proved cerebrospinal fever in the Royal Navy. All of these patients were treated with serums and survived for at least ten days. Out of the 96 cases, 58, or 60 per cent., had a serum reaction as judged by the appearance of the rash. Among these 58 there were 9 (15.5 per cent.) in which the rash was preceded or accompanied by a recrudescence of the meningeal manifestations, suggesting a relapse of the disease. These symptoms were relieved by lumbar puncture, and, under the impression that they did point to a relapse, a fresh injection of serum was given in 6 of the 9 cases. The 3 cases not injected recovered. Of the 6 patients injected intrathecally 4 died. It had been shown by Neal and others that the injection of serum into a healthy or very slightly inflamed intrathecal space sets up an aseptic chemical meningitis, characterized by edema of the meninges, and shown clinically by fever, rigidity of the neck and other signs of meningeal irritation. In a patient with signs of meningeal irritation it is important to be able to decide whether there is a genuine relapse which will be benefited by serum or whether the condition is one of meningism and a manifestation of serum disease which will be intensified by a further injection of serum. The diagnosis between these two conditions can be made by examining the fluid for the presence of meningococci and also for glucose. The latter is absent in true relapses but present in meningism due to serum sickness. Rolleston's statistics at first glance seem to confirm Flexner's statement that meningism is more frequent after intrathecal than after subcutaneous injection of serum. However, Rolleston believes that the serum he used was especially effective in producing a serum reaction, and, from an analysis of his cases, he concludes that the reaction is not more frequent after intrathecal than after subcutaneous injection. In the cases here reported the serum sickness cannot be ascribed to the large quantities of serum employed, for 8 of the 9 cases received less than 100 c.c., and of these 4 received less than 50 c.c. The intrathecal injection of serum necessarily involves some risk of inducing increased intrathecal pressure and may introduce a secondary infection. Rolleston's observations fail to confirm the suggestion of Netter and Salanier that the volume of the serum injected favors secondary infection of the meninges by pneumococci from the blood stream.

The Bruck Precipitin Test for Syphilis.—Stillians (*Jour. Am. Med. Assn.*, 1917, lxix, 2015) performed the Bruck test, according to the author's technic, in 209 cases. In 53 of these (over 25 per cent.) the results disagreed with those of the Wassermann reaction. In 13 cases of active early syphilis, in all of which the Wassermann reaction was very strongly positive, the new test was negative. On the other hand, 24 per cent. of 74 non-syphilitics gave positive Bruck reactions. These occurred in 1 febrile case (septicemia) and in 16 afebrile cases, comprising 1 case of gonorrheal urethritis, 1 of gonorrheal arthritis, 1 of xanthoma planum et tuberosum, 1 of systemic blastomycosis, 1 of dermatitis venenata, and in 1 healthy man, 3 nursing and 8 pregnant women, all apparently healthy. Stillians concludes that the Bruck precipitation test for syphilis fails in a considerable percentage of early secondary syphilis and that it gives positive reactions in from 24 to 28 per cent. of non-syphilitics.

OBSTETRICS

UNDER THE CHARGE OF

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Labor Obstructed by Ovarian Cyst.—SALISBURY (*Jour. Obst., and Gynec., of British Empire*, June-August, 1916) reports the case of a multipara who had been six days in labor, with acute pain, the membranes having ruptured two days previously. She was at full term. On admission, strong uterine contractions were present, with signs of exhaustion. Thirty ounces of urine were withdrawn by the catheter. The child was dead and the head fixed in the pelvic brim. A large, tense cyst filled Douglas's pouch completely below the presenting part, and no attempt was made to displace it. The patient was given stimulation and sedatives, and, when her condition improved, operation was performed. A dermoid cyst of the left ovary the size of an ostrich egg was withdrawn from the pelvis with some difficulty and ruptured during its extraction. The cyst was removed, the uterus replaced in the abdomen, and the fetal head pushed into the pelvic brim. The patient was then placed in the lithotomy position, the occiput manually rotated to the front, and a dead child was delivered with axis-traction forceps. The abdominal wound was then closed, and the patient made an uninterrupted recovery. A second case was that of a woman who had been confined to her home by a midwife who felt a mass behind the vagina and the fetal head high up in front, strong pains being present without progress. After some delay a living child had been born and the pelvic mass had disappeared. The patient vomited once and had some abdominal pain. During the day the patient felt comfortable and was sent into the hospital the next morning. On admission she stated that she was comfortable, but the pulse was quick and there was distinct tenderness on deep pressure over the abdomen. The abdomen was opened and serous blood and mucoid material were present. A semisolid, multilocular cyst adenoma of the left ovary, weighing two and one-half pounds, was found to have ruptured, and one loculus was still lying in the pelvis. The cyst was removed, the fluid mopped up, and a drain inserted. The patient made an uninterrupted recovery. In the third case, as labor commenced, a physician found two polypi in the vagina. On admission to the hospital a small cyst of the left ovary was found to move freely over the left surface of the uterus. A vaginal examination revealed two polypoid adjacent to old scar. Dilatation of the cervix had not commenced. In Douglas's cul-de-sac there was a tense, hard mass the size of a hen's egg, continuous on the left side of the pelvis, with a soft cyst. The mass was immobile and had been diagnosed as a dermoid cyst of the right ovary. Before operation a quantity of liquor amnii escaped through the vagina. When the abdomen was opened the pelvic mass could not readily be approached, so the uterus was first emptied by Cesarean section and a living child delivered. The pelvic

mass was a dermoid of the right ovary, the size of a cocoanut, afterward found to contain bone and teeth. A dermoid of the left ovary was also present above the pelvic braim. Both cysts were removed and the patient made an excellent recovery.

Labor Complicated by Face Presentation.—TITUS (*Surg., Gynec., and Obst.*, December, 1916) writes concerning face presentation in which posterior rotation of the chin into the hollow of the sacrum occurs. He reviews the literature of the subject and quotes a case operated upon by symphsiotomy in 1903. He also describes 2 cases, which have been reported, in which this treatment was carried out. He believes that a reasonable test of the second stage of labor should be allowed to these patients in the hope that anterior rotation will take place. He finds that attempts to rotate by forceps are dangerous to mother and child and that Cesarean section has a high mortality in these cases. If the child is dead or dying, craniotomy is permissible, although this may be difficult. He believes that pubiotomy is the operation of choice where the chin rotates posteriorly and the child is living and in good condition. About twenty years ago, at a time when American obstetricians were doing symphysiotomy, the reviewer had a series of 8 cases of symphysiotomy for disproportion between fetus and mother. In the *Medical News*, a medical journal not now existing, he published a paper in which he advocated symphysiotomy for posterior rotation of the chin in face presentation, and stated his intention to perform the operation should such a case present itself. This did not happen, however, and symphysiotomy was abandoned for other procedures.

The Care of Pregnant Women.—At a meeting of the Section of Obstetrics and Gynecology, Royal Society of Medicine (*British Med. Jour.*, Novenber 11, 1916), a discussion upon this subject was opened by MOORE. He estimated that in England and Wales 3500 deaths occur from childbirth each year. A study of the conditions producing these deaths showed that a very large percentage might be prevented. As a remedy he would advise notification by the patient of her pregnant condition so that she could without fail receive competent medical care. This had actually been tried out in the town in which he lived, a small fee being paid to doctor or midwife for the notification which was only allowed with the consent of the woman herself. In 1536 labors occurring among these patients, 156 of the pregnancies, or 10 per cent., had been notified and received attention during pregnancy; of these, 130 were uncomplicated and 26 required special attention. ROUTH stated that at Queen Charlotte's Hospital in one year 557 cases of albuminuria were admitted. The study of statistics shows that there are 30 per cent. of stillbirths and that it is not at all uncommon to have the birth of a macerated fetus occur. Thus, 25 per cent. of stillbirths show this condition. He believed that care should be given the woman during pregnancy and that postmortem should be made on all stillborn children and search instituted for the characteristic germ of syphilis. BERKELEY described a plan for the establishment of maternity centers which should give supervision of pregnant patients and secure proper care for them and proper attendance during labor. He estimated that 50 per cent. of all pregnant women engaged mid-

wives, and among working women, 75 per cent. BARRETT considered it essential that not only should there be a hospital center, but a local center as well. Much can be done by visitors in the houses of patients who can obtain their confidence. Three activities were necessary: medical, educational and social. The medical needs were three: supervision during pregnancy, attention during labor and supervision during lactation, and for these an obstetric specialist should be available for each mother. On the educational side knowledge concerning healthy pregnancy, delivery and infancy should first be given at a center and afterward repeated in the home of the patient. On the side of social service suitable houses and appliances must be provided for care during parturition. In cases in which no room in a house could be set aside for the use of the parturient woman, hospital conditions were necessary. The pregnant woman should be relieved of the burden of household work in the interests of herself and the child. At the hospital center there should be consultation clinics for maternity cases, infants and children up to school age and prematernity beds and provision for pathological study. MUNRO KERR divided all pregnant women into three groups: (1) Those who were abundantly able to secure good care; (2) a large number of the lower middle class where complications sometimes developed which could usually be cared for without difficulty; (3) the lowest class in the social scale who could not be reached by appeals but who must be governed by legislation. He believed that notification of pregnancy to the patient's physician should be made compulsory and that after the confinement had occurred a report concerning the case should be sent to the medical officer of health. As a penalty for not obeying this law there should be a reduction in the maternity benefit. KRIVSKY, of Petrograd, reported on the conditions in Russia. In European Russia in fifty central provinces there had been a decline in the birth rate from 49.9 per cent. per 1000 in 1894 to 1896 to 43.1 per cent. per 1000 in 1913. The death rate had also lessened from 36.3 per cent. per 1000 in 1892 to 1895 to 27.4 per cent. per 1000 in 1913. The natural increase in the population during this period was 15.7 per cent. per 1000. There was a high mortality among children under one year of age, namely, 27.2 per cent., which was in marked contrast with the same rate in Sweden, 7.1 per cent.; Norway, 6.7 per cent. In 1913 there were 5,249,677 births reported, among which were 870,000 miscarriages and stillbirths. In Russia there were needed for lying-in women 37,000 beds, and to attend the poor, 60,000 midwives instead of the present insufficient number, 14,761. In 1912, 7,033,507 children were born living, and of these 25,240 were born in lying-in hospitals. To show how insufficient is the medical care of this population, 95 per cent. of these confinements were without any obstetrical help whatever. From the stand-point of the midwife PAGET thought that four things were necessary: the early registration of patients, modern teaching for midwives, facilities for medical treatment and the selection of the right sort of person to train as midwives. If compulsory notification were established it would prevent the early registration of these cases. Midwives would do their part in improving the public service if they were given a chance to coöperate with the authorities.

Treatment of Placenta Previa. — HELLIER (*British Med. Jour.*, November 11, 1916) in treatment of placenta previa discussed the field of Cesarean section. He believed that the majority of obstetricians agree that when a patient has had one well-marked hemorrhage that the pregnancy should be terminated without delay. If the patient was not in labor and uninfected and the services of a competent obstetric surgeon could be procured there was much in favor of Cesarean section. He described the case of a patient who had a severe hemorrhage who was treated expectantly, and who died during a second hemorrhage while an attempt was made to perform version. In two other cases he had operated so soon as hemorrhage occurred, with the best results for mother and child. He believed that these patients should be immedately sent to a hospital so soon as a hemorrhage developed. This did not mean that all should be treated by section, for many could be delivered in other ways, but the facilities of a hospital are necessary in the treatment of these cases.

The Morphin-hyoscin Method of Painless Childbirth. — HAULTIN and SWIFT (*British Med. Jour.*, October 14, 1916) published their clinical experience at the Royal Maternity Hospital, Edinburgh. They make no distinction between scopolamin and hyoscin, and use the latter. They had 40 consecutive cases, and while they could not give each a separate room, they darkened the room by placing a screen about the patient and stuffed the patient's ears with cotton to prevent hearing. The first dose given was usually $\frac{1}{4}$ grain morphin, $\frac{1}{150}$ grain hyoscin. Hyoscin alone had no control over pain. In 3 cases only was the morphin repeated. In the remainder the hyoscin was repeated, the average number of injections of hyoscin in each case being eleven to twelve. The greatest number of injections in all was forty-five, which included two doses of morphin. The results were total amnesia and analgesia in 30 out of 40 cases, or 75 per cent. Because the patient could not remember the pain of labor, she asserted that she had no pain when questioned after labor had ceased. There was some effect in all the cases. In 1 case restlessness was so great that the injections were stopped. In 1 case there was postpartum hemorrhage. In 14 cases it was necessary to use forceps, and in 5 of these no chloroform was given. In the other 9 cases when the attempt was made to interfere with the patient, she became restless and it was necessary to use chloroform to apply forceps. There were 5 stillborn children among 40. In one of these cases only had the labor been normal. Among 35 children born living, 4 required artificial stimulation. In using this method the writers think that in a primipara one must wait until the os admits two fingers, and the pains are regular; in a multipara the injection should be given at once. The second injection, $\frac{1}{150}$ grain of hysocin, is best administered an hour after the first. It is thought that this can be safely repeated at intervals of one hour or three-quarters of an hour afterward. The reader is cautioned not to repeat the morphin in the latter part of the second stage, and that if the hyoscin is not taking effect it is well to give the mother a slight whiff of chloroform so that the hyoscin is allowed to work and the patient goes again into the "twilight sleep." The patient's friends must be kept away absolutely and the room kept quiet and dark.

Patients if thirsty must be given water to drink. The catheter must be used during long labors. The baby must immediately be taken away after birth so that the mother cannot hear its cries, otherwise she will remember the labor. This seems a most extraordinary narration and illustrates the remarkable acumen of the scientific gentlemen who carried out the experiment and the extraordinary credulity of their patients. The percentage of forceps deliveries is that usually seen with or without these drugs, and the writers assert that they use forceps frequently. Nothing is said concerning lacerations, and the percentage of fetal asphyxiation is practically normal. The statement is made that pain is not prevented but that forgetfulness is induced, and that what one does not remember does not hurt. We have long been accustomed to look to Scotland for subtle pyschology, and we welcome in obstetric practice this extraordinary contribution to the psychology of parturition. Not having the subtle intellect of the Scot, we fail to recognize its physical value.

Perineal Anesthesia in Labor. — KING (*Surg., Gynec. and Obst.*, November, 1916) reviews the anatomy of the perineal region, and based upon this, has used a 2 per cent. solution of novocain to which is added $\frac{1}{3}$ minim of 1 to 1000 solution adrenalin chlorid to each cubic centimeter. The landmarks are obtained by palpating the pubic arch, and the site of injection is prepared by washing with alcohol or benzine followed by tincture of iodin. The site of each injection is slightly sprayed with ethyl chlorid. The perineal region is divided into two triangles, anterior and posterior, and in the anterior region the needle is entered from 2 to 4 cms. above the lower margin of the vagina, and 2 cms. from the rami. The needle is passed through the fascia, and 1.5 c.c. of the 2 per cent. solution are used for each injection. In the posterior triangle the site of injection is on a line drawn through the anus, and the needle is inclined laterally, entering mid-way between the anus and tuberosities. The injections are made bilaterally. Primiparæ require only the anterior injection, but multiparæ usually need both anterior and posterior. The only unfavorable result seen after this method of treatment consisted in slight superficial necrosis of the inner portion of the labia, but this cleared up without harm. Anesthesia began in a few minutes and was prolonged from two to four hours. Lacerations were diminished in number and extent, and hemorrhage from lacerations greatly diminished. Repair was made much easier because the tissues were not sensitive. The method of sterility employed proved to be practical and satisfactory, and can be readily carried out in private houses.

The Application of Anoci-association to Obstetrics.—HOAG (*Surg., Gynec. and Obst.*, November, 1916) has applied to obstetrics the principle of anoci-association which has received attention in surgery. He combines with this anesthesia by nitrous-oxide oxygen. The objections made to this method have been a lack of muscular relaxation in manipulation, and difficulty in carrying out the principle of local nerve-blocking; 30 cases received perineal injections; 20 were given nitrous oxide; only 4 were given nitrous-oxide and oxygen until the time of delivery, when chloroform or ether was given, and 6 received chloroform in the usual

way. The perineum in all cases was injected with 0.25 per cent. novocain, varying from 60 to 150 c.c. Eleven of the patients received in addition from 30 to 40 c.c. of 1 per cent. quinin-urea solution. In any case the maximum amount of the two solutions injected was 175 c.c. The injection was made as the head appeared in sight; the edges of the vulva were turned back and a long needle inserted at the junction of the skin and mucous membrane, the fingers of one hand being in the vagina to note its position. At this stage of labor the perineal floor is flattened out by the head, but not stretched to any degree. Experience shows that there is no difficulty in infiltrating the levator ani muscles and the perineal body. Novocain was injected first and the quinin-urea immediately afterward. A group of 20 cases were treated by nitrous-oxide oxygen only, and of these 17 received from one to five doses of scopolamin during the first stage before the gas was used. The initial dose was $\frac{1}{200}$ grain with $\frac{1}{6}$ grain morphin or $\frac{1}{2}$ grain narcophin. The scopolamin was repeated during labor. In 4 cases where labor was prolonged a second smaller dose of morphin or narcophin was given. No effort was made to secure the mental condition known as "twilight sleep," because a clear state of the mind is necessary for the successful use of gas. The gas was given before the end of the first stage or at the beginning of the second, according to the distress of the patient and her ability to pay for the gas. The private cases who received this treatment had professional anesthetists, understood exactly what was attempted, and suffered very little. The clinic cases did not do so well. They were not relieved of pain, and with many of them ether or chloroform had to be used. During the actual stage of expulsion complete anesthesia for a few moments was secured. Apparently labor was somewhat shortened by this method, the use of the forceps was no more frequent than with other methods, nor were lacerations more frequent or extensive. In a few cases the injections produced edema and tenderness in the tissues, but no complication developed which interfered with the healing of the lacerations. There seemed to be better dilatation and relaxation of the perineum. In no case could it be proved that the method injured the child. The conclusions of the writer are that the use of small quantities of scopolamin during the first stage of labor is a distinct advantage, shortening the time during which gas is required and giving a much better result. The injection of the perineum seems also desirable. This combined treatment is called by the writer "anociation," and is thought to promise well in obstetric practice.

Combined Tubal and Uterine Pregnancy.—SULLIVAN (*Jour. Am. Med. Assn.*, March 17, 1917) reports the case of a woman in her fourth pregnancy who, while doing housework, had violent pain referred to the diaphragm. This was relieved by morphin, and examination showed the uterus somewhat enlarged, while nothing abnormal was found in the cul-de-sac or abdomen. Two hours later an indistinct mass could be felt in the cul-de-sac. The patient was removed to the hospital and operation performed. In the pelvis and cul-de-sac were clotted blood and a fetus. These were removed, the bleeding tube ligated, drainage inserted, and the abdominal wound closed. By palpating the uterus the outline of a fetus could be felt within its cavity. The patient recovered well from the operation and did not abort. She subsequently gave birth to a vigorous male child.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Traumatic Sympathetic Ophthalmia. — POULARD (*Ann. d'ocul.*, December, 1917, p. 697) resumes his attacks upon current ideas regarding the danger of sympathetic ophthalmia and preventive treatment of the same by enucleation of the injured eye. He shows the inconveniences which follow enucleation as regards the appearances of the subsequent prothesis which are always bad and frequently entail grave prejudices to the wearer to the extent even of affecting his means of gaining a livelihood. He would substitute for this operation a partial ablation, the results of which are better from every point of view—mobility, absence of depression at the orbital margin, etc. He believes there is an unwarranted fear as regards sympathetic ophthalmia in the minds of many ophthalmologists. Hence arises the utterly unjustifiable opinion that this is a disease of daily occurrence, an habitual complication of wounds of the eye. As a matter of fact it is at the present time a rare disease; most oculists have never seen a case. He himself, although exposed to meeting it, in that he does not practise preventive enucleation, has seen but a single instance several years ago, and that in the practice of a colleague. He details this case at length in a separate article (*Annal. d'ocul.*, December, 1917, p. 702): An officer was wounded in the eye April 30, 1915; the latter harbored a foreign body. Preventive enucleation was practised forty days after the wound. The other eye remained healthy for four months, when the signs of sympathetic ophthalmia appeared which terminated in total blindness in two months. He presents this deplorable instance to the consideration of both those who do and those who do not believe in the frequency of sympathetic ophthalmia, and emphasizes the appearance of the first symptoms four months after preventive enucleation. In reply to these strictures, Morax, in the same journal, p. 705, tabulates a series of cases of sympathetic disease, from which he draws the conclusion that to be a certain preventive of sympathetic ophthalmia, enucleation must be practised during the two weeks succeeding infection of the ocular globe.

Continuous Prolonged Treatment by Mercury in Grave Forms of Ocular Syphilis.—ABADIE (*Ann. d'ocul.*, December, 1917, p. 734) remarks that notwithstanding the discovery of arsenobenzol the manifestations of syphilis upon the part of the nervous system, particularly of the optic nerve, are much more frequent and severe than formerly and appear to be becoming more so. To what is this due? Certain writers

ascribe it to weakening of resistance of the nervous system, from the strain of modern life. In support of this view, they call attention to the fact that although syphilis is extremely widespread in the Orient, it rarely attacks the nervous system of those apathetic peoples. He is himself inclined to adopt another explanation: syphilis, all are agreed, is becoming more and more widespread, and the successive and rapid passage of the spirochete from one individual to another may serve to increase its virulence, just as Pasteur was able in an identical manner to augment the virulence of the virus of rabies, but whatever be the reason, atrophy of the optic nerve and chorioretinitis of syphilitic origin, the prognosis of which is regarded as most somber, are of daily occurrence. He believes that it would be less so if two factors in the treatment were more thoroughly utilized: (1) the mode of administration of mercury, (2) perseverance and continuity of treatment. As regards the first of these, there is no doubt but that intravenous injections of cyanide of mercury in doses of 1 c.c. are curative of syphilitic manifestations which resist all other methods of administering the drug. As regards the second point, he thinks that the injections should be persevered in until 30, 40, or even more have been given at progressively lengthened intervals. In the great majority of cases, these infections are well supported; so long as this is the case they should be continued. He has treated a considerable number of such cases for the past twenty years, giving the injections as required. Some cannot go longer than three months without treatment, while others remain stationary one, two or three years without the same when lowered visual acuity gives the signal for further injections. No doubt great perseverance is required both on the part of the patient and surgeon; but this has its reward in that it saves from blindness.

Do Moving Pictures Injure the Eyes?—BAHN (*Ann. Ophthal.*, No. 3, xxvi, 427) comes to the following conclusions in regard to this question, which is frequently put to the ophthalmologist: Moving pictures, under favorable conditions, do not cause as much fatigue as the same period of concentrated reading. When ocular discomfort is complained of there is usually some ocular defect. When there is no such defect at least four sittings of one and one-half hours each per week can be tolerated without discomfort. Under favorable conditions, moving pictures cause increased fatigue, which, if continued, becomes unpleasant and may be harmful, a condition which is greatly increased by prolonged fixed staring at one spot on the picture, a practise which should not be indulged in. A review of the literature records no permanent harm to the eyes from moving pictures. The fact that 10,000,000(?) persons enjoy moving pictures daily, with no definite reports of specific harm or injurious effect, and with but few complaints of slight inconvenience, prove that the moving pictures can have no injurious effects upon the eyes.

Etiology and Treatment of Iritis.—In a discussion upon this subject before the Ophthalmological Section before the Royal Society of Medicine, England (*Arch. Ophthal.*, November, 1917, p. 572), the president, Mr. W. LANG, in opening, pointed out how desirable it was to arrive at some agreement as to the cause of iritis. In an analysis of 200 cases he

found that the causes and their percentages were as follows: syphilis, 6 per cent.; gonorrhea, 12 per cent.; tubercle, 11 per cent.; general affections, 8.5 per cent.; other causes, 25.5 per cent.; pyorrhea, 37 per cent. Hospital figures would probably show a higher proportion for syphilis than 6 per cent., though recent methods of treating that disease would probably place it lowest in the causes. The percentage for gonorrhea was also probably low, but recent knowledge of that disease, resulting in the treatment of the genito-urinary system, where the gonococcus was so apt to lurk, would largely prevent gonococcal iritis. Relapses seem to be largely due to pyorrhea. The sexes were equally affected where tubercle was the cause. Tubercular iritis should be treated as tubercle elsewhere plus local measures to subdue inflammation and to prevent closure of the pupil. In 17 of the cases the patient had either gout or diabetes or herpes of the fifth nerve, or influenza, or pneumonia. Ten had a septic surface on the skin or a mucous surface or cavity; 6 had disease of the tonsils, 23 some affection of the alimentary tract and 7 had trouble in the genito-urinary system. In 1 patient the iritis followed a smart blow on the eye and another had iritis as a sequel of sympathetic ophthalmia. In 74 of the 200 patients there was no discoverable cause except pyorrhea. Removal of the defective teeth or stumps was followed by a rapid clearing up of the iritis. In 22 other cases pyorrhea existed as a complication of other conditions. Of the 74 cases with pyorrhea alone the women were twice as numerous as the men. As 28 per cent. of the patients had septic mouths the aid of the dentist would be of great value.

Tension in Normal Eyes before and after Tonsillectomy.—CARR (*Arch. Ophthal.*, January, 1918, p. 46) has examined 100 cases to determine what effect if any the hemorrhage, anesthetic and shock of tonsillectomy have upon normal intra-ocular tension. A number of cases of iritis with secondary glaucoma had shown a marked and permanent lowering of tenson, along with striking improvement in the iritis, within twenty-four hours after removal of abscessed tonsils. No tension changes had occurred in the fellow eye. The connection between the infected tonsils and the eye lesions seemed clear, yet it was thought best to make a control study of tension in normal eyes before and after tonsillectomy. The material comprised 100 cases of tonsillectomy in patients with no history of eye trouble, with ages ranging from fourteen to sixty-seven years. Pus was expressed from the tonsil in practically every case. The tension was taken under holocain with the Schiotz tonometer, first a few hours before and then twenty-four hours after the operation. In 95 per cent. of the cases practically no variation of the tension was noted. The average tension of the 100 cases was $17\frac{1}{4}$ mm., the lowest 10 mm., the highest 26 mm. His conclusion is that tonsillectomy does not have any effect upon normal intra-ocular tension.

Etiology and Pathogenesis of Chalazion.—DEL MONTE (*Ann. d' ocul.*, October, 1917, p. 607) in an extensive study of this subject concludes that since the Meibomian glands possess no intercommunications a microparasite which gains entrance into one only or several is unable to directly affect the others, but when the epithelium is destroyed and the microörganisms have been carried by means of the

lymphatics into the tissue of the tarsus it is in this tissue that they will exercise finally their pathogenic action. There are accordingly two stages in the pathogenesis of chalazion: In the first or initial stage the process is glandular (penetration of the microparasite into the gland, lesion of the epithelium, proliferative reaction of the sur-surrounding tissue). This primary process, once completed, is final and cannot be renewed; it is therefore limited in time and space, restricted in extension and of brief duration. The second stage, that of diffusion, is extraglandular (transportation of the microparasite into the healthy tarsal tissue, lesion of tissue, proliferative reaction and secondary alteration of the Meibomian glands). This stage may continue for a longer or shorter period, depending upon the pathogenic activity and the possibility of diffusion of the parasite. The process which terminates in the formation of a chalazion may be thought of as follows: Hydration, edema and decomposition (Meibomian epithelium in the initial stage and tarsal in the secondary process or stage of diffusion). Proliferative reaction and formation of a granulomatous nodule, of which the remains of decomposed tissue occupy the center. As regards the manner of action of the parasite it may be stated that it produces a primary lesion, that is to say a kind of necrobiosis or toxic hystolysis which is followed by proliferative inflammatory reaction.

OTOLOGY

UNDER THE CHARGE OF

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Injury to the Ear from High Explosives.—WILSON (*Tr. Am. Otol. Soc.*, vol. xiv, Part II) says the ear stands in a different relation to concussion than any other organ of the body. It is a peripheral mechanism fundamentally affected by varying pressures and especially adapted to register and transform minute pressures into nerve impulses. The nerve impulses are carried to the central nervous system to be there interpreted and utilized—not in one long undivided path but along a path broken at numerous junctions or synapses. At these synapses, communications can be established with other physiological systems. The vestibular system is another finely adapted pressure mechanism, designed to register and signal to the central nervous system pressures produced by movements of the head; here also there is not one unbroken path but an interrupted mechanism with many complex associations with other paths. The symptoms associated with loss of hearing from high explosives are varied and complex. There are present, for instance, headache, sleeplessness, lethargy, tremors, vasomotor disturbance, and exaggeration of tendon reflexes. There is unsteady equilibrium with vertigo. There is concentric narrowing of the fields of vision. In many

fields of anesthesia are present. Hyperesthetic areas are occasionally demonstrable. Speaking generally, one may say that we have here symptoms frequently and advantageously grouped under the term "traumatic neurosis." As a result of the high explosive with enormous and sudden increase of pressure in the ear there occurs a dissolution of the permanent auditory pathway and a spread of the nerve impulse into other adjacent paths. The auditory stimulus no longer reaches its goal and deafness results. Such a dissolution may occur at one or several synapses. It may not be complete and a maximal stimulus may still be able to get through. To help the reëstablishing of the normal we have the fact that habit and association of activity facilitate transmission of impulses. Nerve impulses tend to pass over an accustomed and long established path, so the most favorable cases are those in which complete dissolution has not occurred. The most unfavorable are those where there has been complete dissolution and total deafness to tuning-fork, voice and noise, no matter the intensity of pitch. The treatment is stimulative of normal function: (1) Tuning-forks are applied at first to the bone; after these are readily perceived, sound is conducted through resonators attached to the ear by a tube and finally through the air. In the worst cases the time given varies with the amount of deafness. Intensity plays little or no part, summation of the stimuli being the effective means. (2) As early as possible the voice is used, at first through resonators with tube in ear, then through speaking tubes and finally without any aid. (3) Each period of treatment is short, for fatigue is rapidly produced. If the treatment is too long there will be headache, vertigo, sweatings and occasionally pain in the ear. (4) As soon as possible carefully graduated physical exercises are given. Here the essentials are short duration and no bending. The treatment (except the drill) is given twice a day in the worst cases, and when it is difficult to pass from bone to resonator the piano is used. At each successive stage there must be summation of the auditory stimuli; thus not only must the fork on the resonator be kept up for some time, but with the voice the word must be repeated, and even then there is often a delay before the response comes, it appearing to be not so much that the patient does not hear, but that he hesitates to attach the word to the sound, for if asked what he thinks it is he frequently answers correctly. In an ear totally deaf to the voice, if the semicircular canals are active, there is justification in continuing treatment for some time. The author concludes that: (1) The normal stimulus (musical notes or voice) is an adequate stimulus for the nerve and is the best stimulus. Electricity is contra-indicated and likely to do harm, since it so easily produces vertigo. (2) In the totally deaf, bone conduction is perceived before air conduction. It is essential to differentiate vibrations from musical notes. (3) In these cases, summation of stimuli plays an important part in the perception of sound. (4) There is a marked diminution of the duration of hearing along the whole series of forks—both through bone and air. This corresponds and exists *pari-passu* with concentric limitation of the fields of vision. Often both improve together. Frequently the field of vision is more retracted on the side having the greater deficiency of hearing. (5) If the conducting mechanism is damaged or destroyed, it not only takes longer to get improvement but complete recovery cannot be expected. (6) Prognosis is good,

as a rule, especially when there is no trauma demonstrable in the peripheral organ, and a normal caloric reaction. The most noteworthy exception met with so far is damage to the seventh nerve. In these cases hearing returns but slowly and so far as we have observed not perfectly, even with a normal drum membrane, little if any signs of middle ear inflammation, and a caloric reaction present.

Radium in Diseases of the Ear.—HARRIS (*Tr. Am. Otol. Soc.*, vol. xiv, Part II) concludes, as a result of an extended investigation, that radium, up to the present time, has failed to be of any considerable benefit in the treatment of diseases of the ear. So far as chronic deafness is concerned it has proved virtually a failure. In the rare cases of intractable tinnitus and excessive vertigo, on the one hand, it can be employed with a reasonable hope of relief by its power of destroying the labyrinth. Finally, so far as malignant growths are concerned, it is of value when they are superficially seated. When deep seated there is nothing sufficiently encouraging to be said of it to warrant its use to the exclusion of operative measures when they can with propriety be adopted. The work that has already been done with it on the ear is not sufficient to condemn it *in toto*, however, and it is to be hoped that other investigators will take it up and give it further thorough and careful trial.

Some Observations on the Bárány Tests as Applied to Aviators.—BABCOCK (*Boston Med. and Surg. Jour.*, December, 1917) sums up the results of more than 1000 observations in the aviation tests for equilibration by means of the American modification of the Bárány chair, and a collaborative determination of the corresponding pulse rate, the summation of the latter, taken in 1000 cases, being as follows: Average pulse rate per minute before turning, 78; average pulse rate per minute after turning, 87; average pulse increase per minute, 9; lowest pulse rate per minute before turning, 58; highest pulse rate per minute before turning, 108; lowest pulse rate per minute after turning, 60; highest pulse rate per minute after turning, 124. In 80 cases the pulse rate increased after turning; in 12 cases there was no change; in 8 cases the pulse was lower after turning; the greatest increase was from 80 to 116, or 36; the greatest decrease was from 76 to 66, or 10; These findings cover a wide range of variation. Taking the general average it can be said that in 100 cases the stimulation to the vestibular portion of the eighth cranial nerve end-organ by fifty revolutions, at varying rates of speed, produced an increase in the rate of heart action of nine beats per minute. Taking the cases separately they may mean little or nothing. The responsiveness of the pulse rate to mental conditions probably accounts for the 8 cases which showed a lower rate after turning, due to the fact that some of the men approached these tests with considerable apprehension. In a very few cases an active reflex with the tenth cranial nerve has caused vomiting, especially after stimulation of the vertical canals. In no case has the candidate fainted, although when it is anticipated he is strapped in the chair.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Etiology of Granuloma Inguinale.—This lesion, because of its occurrence in the region of the groin and external genitalia, has often been referred to as a venereal granuloma, though recent studies deny this origin. It is endemic in certain tropical and subtropical countries, and is occasionally found in temperate regions. WALKER (*Jour. Med. Res.*, 1918, xxxvii, 427) had an opportunity of studying a number of cases in Brazil. Specimens were obtained for histopathological analysis, and a bacteriological study was also carried out. From the open ulcers a variety of microörganisms could be demonstrated. In the Giemsa smears, spirochetes of different kinds were commonly present. Interesting cell inclusions were observed in the large mononuclear cells. These cell inclusions varied, some of them appearing like vacuoles while others had the character of stained rods. The author believed that the variety of cell inclusions was the result of disintegrative changes of ingested cells and débris. However, some of the materials bore a close resemblance to the intracellular organisms described by Donovan. This type appeared to be encapsulated and the organism varied from oval bodies to distinct rods. The author was able to isolate from a number of cases an organism having the morphological and cultural characters of the bacillus mucosus capsulatus. A number of animal experiments carried out with organisms belonging to this capsulated group of bacteria gave rise to lesions resembling those spontaneously developing in man. It is suggested that the infection in man is gained through abrasions or develops as a secondary infection with other lesions.

Experimental Perforating Wounds of Abdominal Viscera.—The experience gained in previous wars and in civil surgery has demonstrated the vital necessity of early operation in wounds of abdominal viscera. DRUMMOND and FRASER (*Jour. Path. and Bact.*, 1917, xxi, 457) have sought to learn some of the principles underlying the repair of perforating wounds of the abdominal alimentary canal by producing in hares, cats and dogs wounds similar to those caused by bullets. They have been able to corroborate surgical experience of the protective action of the omentum and of plastic peritonitis between the coils of bowel. They found that, following these sudden scissor wounds, the omentum, being perhaps paretic, was not attracted to the injured point, and they put forth the hypothesis that this positive chemiotoxis occurs only when the bowel has been bruised and not perforated, without offering experimental evidence for such migration of omentum in these animals. When the omentum was attached to the wound at operation, vascular anastomosis between it and the gut wall occurred in seven days, except

that when the duodenum and upper jejunum were perforated, omental grafts were of little value. Another protective feature was the plugging action of a small sacculation of the mucous coat through the wall at the site of the puncture. The authors found that single, and occasionally multiple, small wounds of the stomach and bowel may recover and that wounds of the ileum show a greater tendency to spontaneous cure than those of any other part of the intestinal tract.

A Contribution to the Serological Classification of the Bile-soluble Diplococci.—It is somewhat remarkable that a group of streptococci shares with certain protozoa such as trypanosomes, spirochetes and amebæ, the property of readily undergoing complete solution in the presence of bile or bile salts. So far as is known no other bacterial species shows this peculiarity. Other very definite biochemical features mark sharply this group from the other streptococci, and yet in spite of this considerable confusion at present exists in regard to their differentiation. All bacteriologists agree they are pneumococci, but there is no agreement that all pneumococci are bile-soluble and show the other characters attributed to them. Until recently all the bile-soluble diplococci were regarded as belonging to one species, of which the approved name appears to be Streptococcus lanceolatus, Gamaléia (1888). Evidence is now accumulating to show that it is necessary to divide the groups into two or more species. MAIR (*Jour. Path. and Bact.*, 1917, xxi, 305) regards the causal infective microbe in scarlet fever as a distinct member of the group. To avoid confusion with Klein's Streptococcus scarlatinæ he offers the name of Diplococcus scarlatinæ. The only certain criteria at present available for the distinction of the different species and groups of bile-soluble diplococci are serological. Investigating the etiology of scarlet fever, Mair showed that a bile-soluble diplococcus of a special serological type occurs with great constancy in the throats of scarlet fever patients. This diplococcus on subcutaneous injection into monkeys produces a condition which in several respects resembles a scarlet fever in the human subject. In attempting to differentiate the scarlatinal diplococcus by complement-fixation methods from certain closely related bile-soluble diplococci, which occur with considerable frequency in apparently normal throats, difficulties were met with, and for this reason sera prepared from the rabbit and a precipitin reaction was employed. By means of this test four scarlatinal strains were isolated. Of 100 cases it was found that in about 90 per cent. of scarlet fever cases the Diplococcus scarlatinæ could be isolated in the first week, and by a set of control tests—normal throats—it was discovered that the frequency of the occurrence of scarlatinal carriers is of the same order as that of diphtheria carriers, and is possibly somewhere near 2 per cent. of the general population. More general application of the method here used may show the relationship of these various strains to one another, and so give more information as to their pathogenic action in the various diseases with which they may be associated.

Formation of Bone in Calcified Epithelioma of the Skin, with Some Remarks on Metaplasia.—NICHOLSON (*Jour. Path. and Bact.*, 1917, xxi, 287) reports a case of neoplasm of the skin which had undergone ossi-

fication. As a tumor it is rare and the process by which the bone arises, whether one of metaplasia or differentiation, is of great interest. Briefly described it was a slowly growing and clinically innocent epithelial neoplasm found in the subcutaneous tissue of the pectoral region of a man, aged forty-one years. It was surrounded by a capsule which, however, was incomplete and through which projected a few processes of epithelium. It was squamous in type, prickle cells and intercellular fibers being present. Evidence of keratinization was found. The whole of the tumor was necrotic. The epithelium was calcified, calcification being most intense at the periphery of the acini. The greater part of the stroma was liquefied and had disappeared. A few of the fibers had calcified. The death of the tumor was due to deficient blood supply, as a few thick-walled vessels were present. At a date subsequent to its death a part of the tumor had invaded from the subcutaneous tissue by granulation tissue. This replaced the old stroma and partially removed the calcified dead epithelium by means of foreign-body giant cells. A narrow zone of uncalcified epithelium was often present in immediate contact with the granulation tissue, where its fibroblasts came in contact with the dead masses they acquired delicate processes and laid down bone with lacunæ, canaliculi, lamellæ and Haversian canals. The bone did not extend any distance into the tumor but was limited to the edges of the epithelium, except where it replaced a small calcified portion of the old stroma. Thus we have a squamous-celled carcinoma of the subcutaneous tissue with its origin in a cutaneous cell rest or graft in embryonic life. As for the changes that occurred in the tumor and that culminated in the appearance of bone, they were of two kinds, regressive (necrosis and calcification) and progressive—the invasion of a part of the tumor by vascular granulation tissue, of decalcification and removal of the epithelium by means of foreign-body giant cells and its replacement by bone. The interesting question to be considered is whether the fibroblasts were converted into bone corpuscles by a process of metaplasia or one of differentiation. The fibroblast, especially when in a state of active proliferation, has very slight differentiation and is not (in appearance at any rate) very far removed from the cells of the mesoblast of the embryo. Now metaplasia is the assumption by one differentiated tissue of the morphological structure and functions of another differentiated tissue. It should be clearly distinguished from the differentiation of embryonic tissues. It is usually found apart from neoplasms in association with irritation, mostly of a chronic nature. As the fibroblast is the cell, which of all those in the body is chiefly concerned with repair, Nicholson sees no reason why with unusual stimuli it should not be able to produce some of the mesoblastic tissues, bone for instance. Metaplasia is a term he believes which should be reserved for a metamorphosis and should not be extended to a simple differentiation.

Immunity by Transplanting Tuberculous Lymph Nodes into Animals.—The authors of this research, WEBB, RYDER and GILBERT, state (*Am. Rev. of Tuberculosis*, 1918, i, 693) their hypothesis as follows: "If bacilli instead of being injected free into tissues, with no special capacity for resisting or detaining them, were introduced into the substance of a

tissue supposed to have a special defensive function against them, and already in a state of reaction to them, the results might show some diminution of virulence or some increase in immunity in the new host." Guinea-pigs were used in the experiments. The first series of animals were inoculated subcutaneously with 300 bacilli and a month later the inguinal lymph nodes were excised and transplanted subcutaneously into a new series. These animals in turn developed tuberculous lymphadenitis and the inguinal lymph nodes were inoculated into new animals, and so on with succeeding series. The wound of implantation heals in about two weeks, at which time the inoculated tissue is surrounded by a granulation tissue developing from the host. Caseation continues within the node and may ulcerate on the skin surface. From the third to the fifth week the inguinal glands of the host become involved and the animal not uncommonly is overwhelmed with a tuberculous infection as if inoculated by free bacilli. The authors have not been able to determine any increased resistance on the part of the inoculated animals, nor were they able to demonstrate any modification in the virulence of the bacilli. Tuberculin tests are negative until true infection of the tissue of the host has taken place. The implantation of a second tuberculous nodule after the first has been established leads to what appears to be a tuberculin reaction. The difficulty in all these experiments lay in the progressive general infection. In another series of experiments the authors attempted to obviate this difficulty by covering the transplant with a coating of celloidin. The difficulties in these experiments arose from the repeated sloughing of the inoculated mass. In one instance the nodule was retained ten months. This animal showed no evidence of disease, and repeated tuberculin tests were negative. They were able to demonstrate diffusion from within the celloidin coating by transplanting a large tuberculous node beneath the skin of a tuberculous guinea-pig. A reaction developed in the vicinity of this node similar to that from tuberculin.

The Etiology and Pathology of Rocky Mountain Spotted Fever.—Wolbach (*Jour. Med. Res.*, 1918, xxxvii, 499) has added a third report to his previous preliminary contributions. He had previously described the lesions in guina-pigs and monkeys. These lesions were essentially those of the vascular system. A microörganism was observed as a minute rod, surrounded by a clear zone and occurring in the endothelial and smooth muscle cells. Similar parasites were found in ticks (Dermacentor venustus). From his further studies the author is convinced that the parasite does not belong to the protozoa nor has it the characters of ordinary bacteria. He suggests that it probably represents a new form of microörganism. The author has had an opportunity of carefully studying 3 human cases of Rocky Mountain fever. In 2 of them there was a history of tick bite a few days before the onset of illness. Autopsy examinations were made in 2 cases and in the third skin from various parts of the body was obtained. The important findings were the presence of extensive vascular lesions in the skin and subcutaneous tissues of all parts of the body. The vessels in the deep cornium and fat are often thrombosed. The earliest lesion is a collection of endothelial cells over a swollen portion of the intima. The elastic

fibers are fragmented. The minute parasite is found in these endothelial cells and in the muscle fibers of the media. Similar lesions are present in the veins. It is noteworthy that the bloodvessels of internal organs do not show this reaction.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Scarlet Fever during 1915 in Philadelphia.—OSTHEIMER (*Am. Jour. Pub. Health*, October, 1916, vol. vi to x) states that during 1915, 1072 cases of scarlet fever were reported in Philadelphia, exactly 100 more than half the number reported in 1914. There is a morbidity rate of 63.7 per 100,000 as compared with 117 in 1914 and 208 in 1913. The lowest number of cases was reported during August, 29 cases; the highest number during December, 147 cases. As to the sex of the 1072 cases, 529 were males, of which 513 were boys and 543 females, of which 501 were girls. These figures are the lowest since 1900, as is also the death-rate from scarlet fever during 1915, which is only 26 in the entire city; 74.6 per cent. of the cases were reported to the Bureau of Health within three days from their onset. Girard College furnished the only institutional epidemic of 31 mild cases, and there were also two small school epidemics of 12 and 10 cases each. No cases were traced to milk infection. Statistics of the number of cases in the different wards and districts were made and it was found that the density of population had no relation to the number of cases. When the primary case was treated at home, 117 secondary cases occurred later than twenty-four hours, but within one month after the first case; but only 31 secondary cases occurred when the primary case was removed to the hospital for treatment. During the year of 1915, 625 cases, or 58.3 per cent., were removed to the Philadelphia Hospital for Contagious Diseases, while 447 cases, or 41.7 per cent., were treated at home. The hospital death rate during the year was 21 deaths, or 3.3 per cent., and the death rate among those treated at home was 5 deaths, or 1.1 per cent.

The Germicidal Effect of Gastric Juice.—GREGERSEN (*Zentralbl. Bakt.*, 1916, Part I, p. 353) found that the bactericidal effect depends wholly upon the presence of free hydrochloric acid. The experiments were carried on with Staphylococcus pyogenes aureus. The bacterial emulsion was incubated with 4 c.c. of gastric juice at body temperature.

In the absence of free hydrochloric acid but in the presence of hydrochloric acid combined with amino groups there is a very slight germicidal effect. The presence of even small quantities of free hydrochloric acid results in a very material increase of the germicidal power, compared to which the effect of the combined hydrochloric acid is insignificant. The effect is in proportion to the quantity of free hydrochloric acid present. It has been found that the free acid present in the gastric juice resulting from Ewald's test breakfast was four times as effective as an equal quantity of free acid in an artificially prepared solution. This is explained by the presence of certain substances in the dry toast which by themselve are not germicidal. These extractives are capable of raising the germicidal power of the free acid present. Pepsin has been found to be of no influence.

A Modification of Roemer's Intracutaneous Method for the Determination of Small Amounts of Diphtheria Antitoxin in Blood Sera.—ZINGHER (*Jour. Infect. Dis.*, October, 1916, No. 4, vol. xix) descibes a convenient, practical and economical test for the determination of the antitoxin content of blood. The test is important in dealing with many experimental and clinical problems connected with the subject of diphtheria. The advantages of such a test are that: (1) The L + dose of the toxin is taken as the test dose and so diluted that each cubic centimeter represents $\frac{1}{100}$ L + dose. (2) Two test points are established with each serum, the test at which no lesion develops, and the one for twice the amount of antitoxin at which a distinct lesion appears; within these two limits lies the antitoxin content of the serum. (3) It saves animals because 4 tests can be made on one guinea-pig. (4) As little as $\frac{1}{200}$ unit of antitoxin can be determined in a serum with a fair degree of accuracy. The details of the test are as follows: (1) A standard, well-ripened toxin is used, so diluted with normal salt solution that 1 c.c. represents $\frac{1}{100}$ L + dose. (2) The serum to be tested is used either undiluted or diluted 1 to 10, 1 to 100, etc. The amount of serum used in the test is always 0.2 c.c. except when the test is made for $\frac{1}{200}$ unit of antitoxin, then 0.4 c.c. is used undiluted and is added to 0.2 c.c. of toxin solution. (3) Normal salt is used to balance the mixture. (4) After putting together the toxin, serum, and salt solution the mixture is allowed to stand for thirty minutes at room temperature before injection into the guinea-pig. (5) Four injections are made in each pig, the abdomen being divided into four quadrants and the injections made as far apart as possible. (6) The places of injection are examined at the end of 24, 48, 72, and 96 hours and the results noted, *i. e.*, whether and to what degree there is redness, induration, or necrosis. In the interpretation of results, the absence of lesion at the site of injection indicates that the serum on test has completely neutralized the toxin solution and contains therefore more than the unit of antitoxin tested for; the presence of necrosis indicates that it contains less than the unit of antitoxin while the presence of a lesion indicates that it contains the unit of antitoxin.

The Control of Communicable Diseases in Schools.—BAKER (*Am. Jour. Pub. Health*, October, 1916, No. 10, vol. vi) states that in time past the school has been accused of being a focus for the dissemination

of infection and the occurrence of the "contagious diseases of childhood" is associated with the beginning of school attendance. But the school with its segregation of the children also offers a great opportunity for early detection of cases of communicable disease. The prevention of communicable diseases by the exclusion from school of children showing any symptoms of such diseases is a very important part of the system of medical inspection of schools. In order that such a system may be effective, the child should be excluded from attendance and isolated before he has a chance to infect others. In New York City the system has been worked out as follows: Each school receives a printed list of all cases of communicable diseases reported to the Department of Health on the previous day. This list is sent to every teacher and the name of each pupil who is entered on the list or who is a member of the patient's family is noted. Such children are excluded from school at once. The names are reported to the school nurse who reports each day to the school inspector. When two or more cases of any disease have occurred in any one class-room, the inspector examines each child in that class-room every morning and excludes suspicious cases. Each school is visited by the school doctor or school nurse each day and every child who shows any evidence of illness is examined by them as well as those returning after illness or an unexplained absence. At this time, any child who shows any symptoms indicating a communicable disease is excluded. Additional preventive measures included in this scheme are a monthly routine inspection of all children in each school and physical examinations with consequent follow-up visits to adjust unsanitary and unhygienic home conditions. During the six years that this system has been in effect, it has not been necessary to close any public school in New York City on account of an epidemic of communicable diseases and out of an average school population of 800,000 children in New York City, an average of five thousand or less than 1 per cent. have been necessarily excluded each year because of the presence of a general constitutional disease. The author concludes with the statement that such medical control of schools may be exercised in any community and the school instead of being the focus for disseminating disease may become a very valuable means of checking the spread of communicable diseases.

Experimental Cholera Carriers.—SCHÖBL in a previous communication showed the relative values of various methods to make cholera carriers of guinea-pigs. The duration of the state of parasitism following intravesicular inoculation, the distribution of cholera vibrios throughout the alimentary canal, and the elimination of cholera vibrios in the feces of the experimental cholera carriers were studied. SHÖBL (*Jour. Infect. Dis.*, August, 1916, xix, No. 2) now reports further studies along these lines and comes to the following conclusions: Sufficient evidence has been gathered, it is believed, to justify the opinion that the condition in question is an infection of the gall-bladder, and that the cholera vibrios injected into and recovered by culture from the gall-bladder stand in causal connection with the pathological changes encountered, instead of merely surviving as saprophytes at the place of inoculation. The infectious process may vary in extent and intensity, remain limited to the gall-bladder or extend to the liver. The absence

of cholera vibrios from blood from the lungs and from the spleen makes the septicemic character of the infection highly improbable. With regard to the intravesicular inoculation the rabbit's behavior differed from that of the guinea-pig, inasmuch as the inflammatory process which followed the injection of cholera vibrios brought about the occlusion of the gall-bladder, so that the cholera vibrios were no longer to be found in the intestine at a time when they were still present in the contents of the gall-bladder. It is evidently a benign process which shows marked tendency to healing, *i. e.*, the cholera vibrios disappear from the animal's body and the animal survives, although a large percentage of the animals showed signs of chronic intoxication.

The Value of Cholera Immunization.—KONRÁDI (*Zentralbl. Bakt.*, 1916, Part I, p. 339) states that following vaccination the blood will show agglutination for about a year. The protection conferred by vaccination depends upon the number of inoculations, the dosage, and upon the mode of living. An annual dose of 0.5 c.c. is sufficient. The vaccination is free from danger even to children. The author employs Kolle's method of preparation of cholera vaccine. The bacterial emulsion is heated for one hour at 55° C. One-half per cent. phenol is added. One c.c. of the emulsion contains 2 mg. of culture. The first dose is 0.5 c.c. An additional 1 c.c. is injected after one week. The symptoms are slight and usually disappear within two days. The author's experience is based upon 1400 immunizations.

The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age.—SILVER, GARRISON and MCNEAL (*Arch. Int. Med.*, August 15, 1916, xviii No. 2) give as their purpose "the presenting of recorded facts in respect to incidence of pellagra and its death rate in the year of initial attacks in each year since the appearance of the earliest recognized case in the county and the correlations between race, sex and age on the one hand and incidence of pellagra and death rate in initial attack on the other, as shown by the total cases on the records at the end of the field work in 1914." The paper deals only with initial attacks and not with recurrences of the disease. The authors studied first the incidence of pellagra in each year, and found that the number of recognized cases in the county had increased progressively each year since 1907, more rapidly up to 1911 and at a less rapid rate up to 1914. As to the death rate in the year of initial attack, they found it to be 15.8 per cent. for the 1180 recorded cases. The death rate was higher up to 1911 but there was no decided indication of a progressive change in it after that time. As the result of their study of the important relation of race, sex and age to pellagra the authors have reached the following conclusions. The death rate in initial attack has been 41.8 per cent. for negroes and 12 per cent. for the white race. It was found that the disease has more severely attacked the white race than the negroes of the county, but that in late years there has been a slow but progressive increase in the ratio of negro pellagrins to white pellagrins. Pellagra has rarely been found under the age of one year, but is not so rare in the second year, and during the period from two to twelve years it is quite common. The death rate in initial attack has been low in

children. In cases of infantile pellagra, evidence of close residence with another pellagrin is usually early noted. The milk of pellagrin mothers is not considered by the authors to be the cause or the vehicle of the cause of pellagra in infants. The period from twelve to sixteen years is relatively free from initial attacks of pellagra. After sixteen years, the incidence of pellagra rises rapidly in women, especially in colored women, among whom the death rate has been 46.7 per cent. in the year of onset during the period from sixteen to twenty years. Between the ages of twenty and fifty years the number of women pellagrins gradually decreases. The number of men attacked gradually increases during this period so that at fifty years the two sexes are about equal. The onset of pellagra in old age has been found to be somewhat more common in men. In white women over twenty years of age the death rate has been found to be 11.9 per cent., increasing progressively from 4.6 per cent. in the third decade to 47.6 per cent. in the seventh decade of life. For analogous groups of white men, colored women and colored men the death rate has been 21.2 per cent., 40.2 per cent., and 50 per cent., respectively, increasing slightly with age in all these groups. A table recording the incidence of pellagra per 10,000 population in respect to race, sex, and age gives the following computations: Incidence per 10,000 for white male population, 231; incidence per 10,000 for colored female population, 81; incidence per 10,000 for colored male population, 25. In the age period ten to fourteen years, the incidence is low in all groups. In white female population it is highest in the age period thirty to thirty-four years, namely, 535 per 10,000. In white male population it is 325 per 10,000 in the period from fifty-five to fifty-nine years. In colored female population it is 241 per 10,000 in the period from thirty to thirty-four, while in colored males it is 33 per 10,000 in the period from sixty to sixty-four years. Another table shows the proportion of initial attacks in children under twelve years of age to be increasing. In 1910 they were only 3.7 per cent. of the total recorded cases, while in 1914 they were found to be 29.7 per cent. of the total recorded cases. In the opinion of these investigators the relatively lower incidence of pellagra among the negroes of Spartanburg County is due to the fact that they are, in a large measure, segregated from white pellagrins and that the disease is not so persistently present among them because they die much more rapidly than do white pellagrins, due to greater poverty and poorer diet. The study of racial and age differences in the incidence of pellagra show that poverty and poor diet are important factors in determining the death rate among pellagrins but that they are important only in connection with close association with antecedent pellagrins if the original onset of the disease is under consideration.

Different Types of Streptococci and Their Relation to Bovine Mastitis.—Mathers (*Jour. Infect. Dis.*, August, 1916, No. 2, xix) finds that hemolytic streptococci of human origin produce mastitis in cows, as Davis and Capps have shown, when injected directly into the milk ducts. This mastitis may be severe, leading to a caked bag and later to a chronic inflammatory condition which results in an atrophy of the mammary gland. On the other hand, virulent hemolytic streptococci may grow and multiply in the milk ducts of a cow without causing

any visible changes in the udder. The milk, however, as these observations show, contains hemolytic streptococci and an increased number of leukocytes. These infections may persist over long periods of time in the form of a chronic mastitis. Streptococcus lacticus of the type used in these experiments produces a very acute inflammation of the udder when cultures are injected directly into the milk ducts. This infection in my experiments was of short duration and left the gland functionally unchanged. A non-pathogenic hemolytic streptococcus of the type commonly found in normal milk may give rise to a transitory inflammation of the udder when injected directly into the milk ducts, producing a mastitis similar in every detail to that produced by non-hemolytic Streptococcus lacticus. The presence of pathogenic streptococci and an increased number of leukocytes in milk is indicative of a mastitis, and may be the sole indication of mastitis. The quarters of a cow's udder under experimental conditions are apparently separate as regards infection. One quarter may be infected while the others remain normal. Examination of the milk from each quarter of the udder is necessary before mastitis can be excluded in a suspected cow. In three instances of bovine mastitis, all of which were due to hemolytic streptococci with all the characteristics of the human types, no noteworthy changes in the morphology or cultural characteristics of the invading organisms were observed in frequent examinations of the milk throughout the course of the infections. The distinguishing characteristics primarily noted for each organism were still present at the last observation, and there were no modifications which might be considered as indicating a change from one type to the other. The cultural and morphological characters of Streptococcus lacticus and of the hemolytic streptococcus derived from normal milk did not change during the course of the udder infections which they induced.

Rocky Mountain Spotted Fever in California.—CUMMING (*Jour. Infect. Dis.*, November, 1917, p. 509) states that the results of animal inoculations definitely establish the occurrence of Rocky Mountan spotted fever in California. The finding of Dermacentor venustus in Ventura County and the occurrence of a case there marks that region as a new area of possible prevalence of the disease in California. Advantage should be taken of the inoculation test to establish definitely the nature of the seasonal eruptive fever which occurs in Modoc and Lassen counties.

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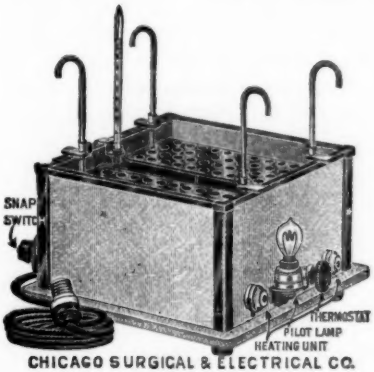

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